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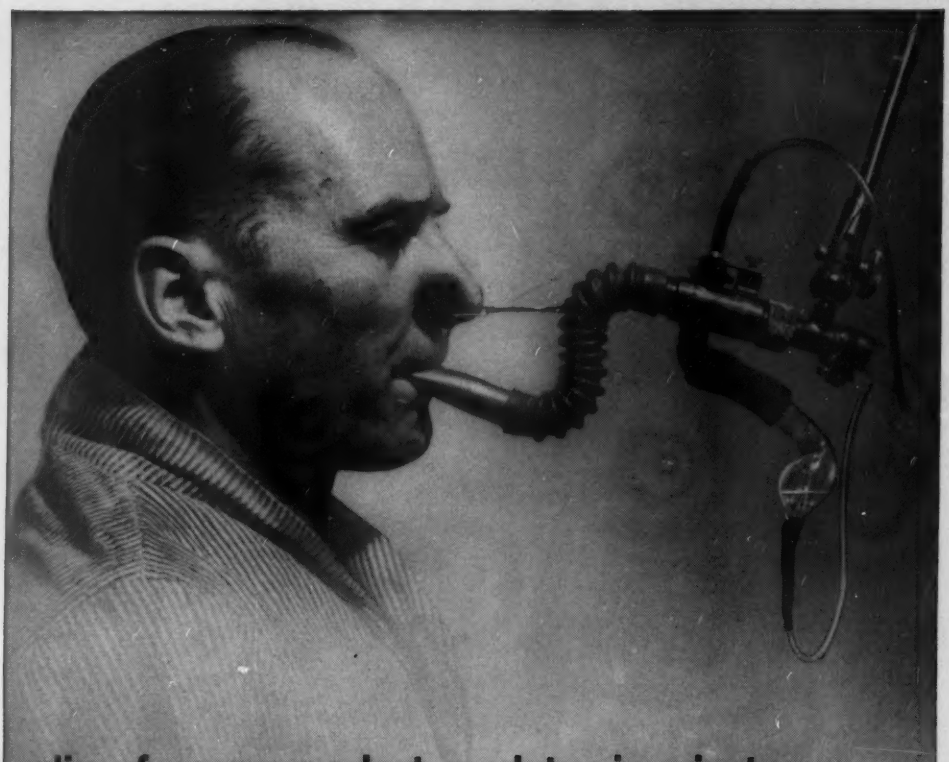

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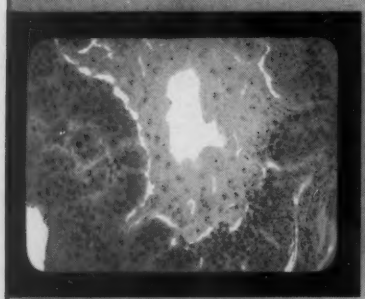

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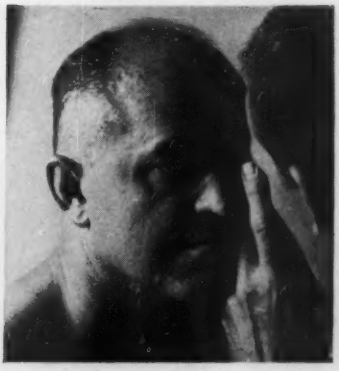

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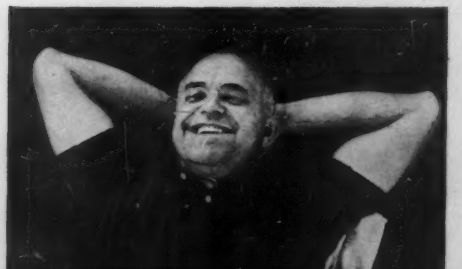

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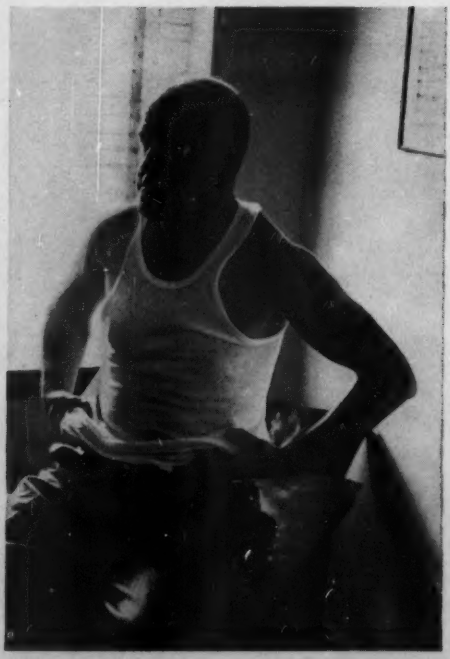

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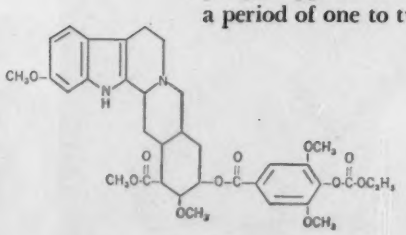

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Dosage: *In New Patients:* Average initial dose, 1 to 2 tablets (1 to 2 mg.) daily. Some patients may require and will tolerate 3 or more tablets daily. Maintenance dose will range from ½ to 3 tablets (0.5 mg. to 3 mg.) daily. When necessary for adequate control of blood pressure, more potent agents may be used adjunctively with Singoserp in doses below those required when they are used alone. *In Patients Taking Other Antihypertensive Medication:* Add 1 to 2 Singoserp tablets (1 to 2 mg.) daily. Dosage of other agents should be revised downward to a level affording maximal control of blood pressure and minimal side effects.

Supplied: Singoserp *Tablets,* 1 mg. (white, scored); bottles of 100.

References: 1. Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: To be published. 2. Wolffe, J. B.: Mod. Med. 26:253 (Feb. 1) 1958. 3. Bartels, C. C.: To be published.

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22½% More Vital Capacity Right Now

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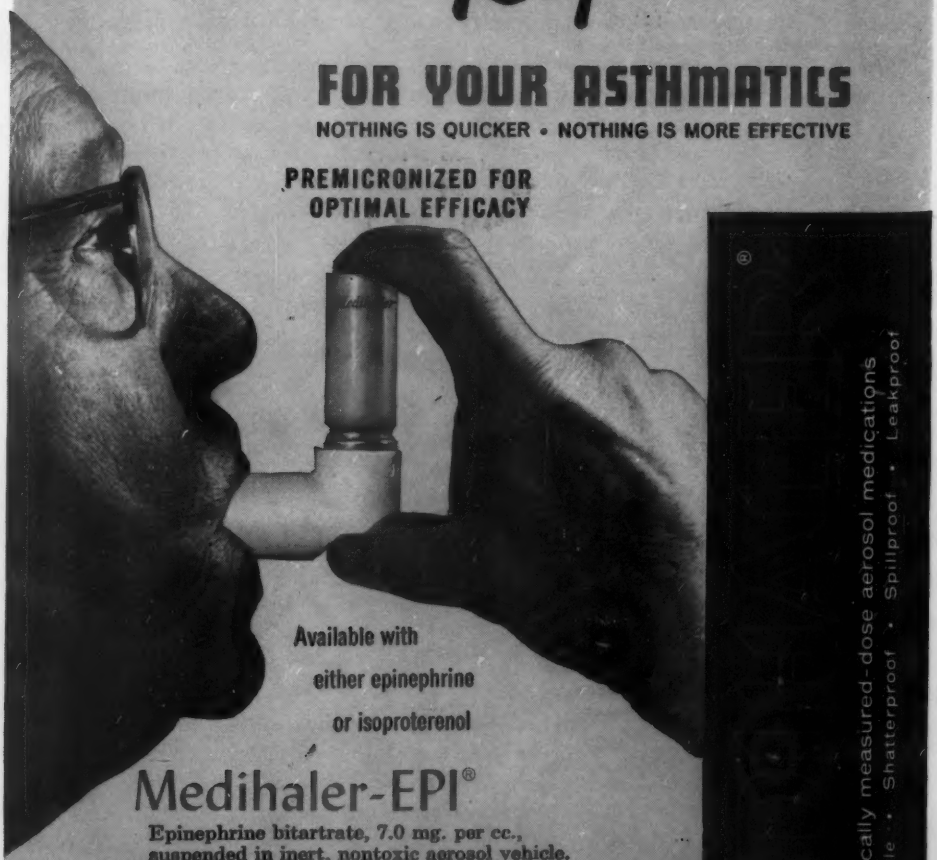

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Medihaler-ISO®

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

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NOTABLY SAFE AND EFFECTIVE FOR CHILDREN, TOO.

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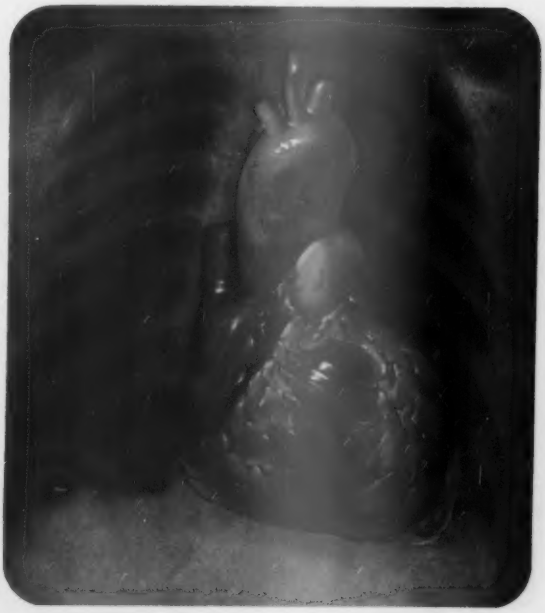
Arteriosclerotic Heart Disease



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FASTER RATE OF ELIMINATION THAN DIGITOXIN OR DIGITALIS LEAF.

THESE SIMPLE DOSAGE EQUIVALENTS MAKE IT EASY TO SWITCH YOUR PATIENT TO GITALIGIN— 0.5 mg. of Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.5 mg. digoxin or 0.1 mg. digitoxin.

Supplied:

GITALIGIN 0.5 mg. Tablets—bottles of 30 and 100.

GITALIGIN Injection Ampuls—2.5 mg. in 5 cc. sterile, I. V. solution.

GITALIGIN Drops 30 cc. bottle with special calibrated dropper.

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Nonbreakable • Shatterproof • Spillproof • Leakproof

FOR UNMATCHED TOLERANCE AND OPTIMAL ABSORPTION

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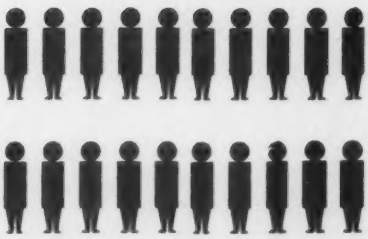
(Molybdenized-Ferrous Complex)

IN IRON DEFICIENCY ANEMIA – SPECIALLY WHEN IRON ABSORPTION IS DEFECTIVE

MOL-IRON...
WELL TOLERATED
by **97.9%**
of 336 patients[1-9]



But 22.4% G. I. side effects with $FeSO_4$

VITAMIN C–"Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid..."[10]

MOL-IRON WITH VITAMIN C TABLETS

Each contains – Mol-Iron (ferrous sulfate 195 mg., and molybdenum oxide 3 mg.) plus ascorbic acid 75 mg. Bottles of 100. Dose – 1 or 2 tablets t.i.d.

1. Brit. M. J. 1:407, 1952. 2. Bull. Margaret Hague Mat. Hosp. 1:68, 1948. 3. Am. J. Obst. & Gyn. 57:541, 1949. 4. Connecticut M.J. 14:930, 1950. 5. J.-Lancet 66:218, 1946. 6. Am. J. Obst. & Gyn. 62:947, 1951. 7. Am. J. Med. Sc. 212:76, 1946. 8. Obst. & Gynec. 5:201, 1955. 9. J. Ped. 41:170, 1952. 10. Ann. Int. Med. 42:458, 1955.

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2 reliable oral anticoagulants

Tromexan

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"...of real value in acute anticoagulant therapy."

- rapid, therapeutic hypoprothrombinemia within 18-24 hours[1,2]
- on discontinuance of therapy prothrombin time returns to normal with exceptional rapidity[4]
- well tolerated

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smooth-acting anticoagulant of intermediate rate of action

- prompt, therapeutic hypoprothrombinemia within 36-48 hours[4]
- prolonged, stable effect evenly sustained with single, low, daily dose[5-7]
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- well tolerated[5,6,8]

(1) Mayer, G. A., and Connell, W. F.: Connect. M. A. J. 17:930 (Nov. 15) 1952.
(2) Burke, G. F., and Wright, I. S.: Circulation 3:164, 1951.
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Tromexan®, ethyl biscoumacetate, Geigy, tablets containing 150 mg. and 300 mg.
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Geigy

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THE RATIONALE FOR THE USE OF VITAMINS IN FORESTALLING INFECTIONS

Many clinicians believe that good nutrition plays a significant role in preventing bacterial infections, and that immunity depends on adequate vitamin levels. Tisdall[1] states that "a low intake of a number of vitamins, a low intake of minerals, and a change in the quality of protein can all lower resistance to infection."

Other studies show the important role of the B vitamins in antibody formation. Thus, *Nutrition Reviews*[2] reports: "Present evidence indicates that certain B vitamins, notably pyridoxine, pantothenic acid and folacin, play a significant role in antibody synthesis." According to Pollack and Halpern,[3] "Under-nutrition leads to increased susceptibility to infection and decreased resistance to established disease." And "vitamin deficiency states also may adversely influence circulating antibodies."

Halpern[4] reports that "good nutrition is important for optimal resistance to infection, for a superior tissue capability to cope with disease and injury, and for maximum antibody production . . . nutrition participates in the prophylaxis against most acute infections . . ."

And while MacBryde[5] feels that evidence is lacking to support the view that a higher than normal intake of vitamins will improve resistance to infection, he also states: "Restoration of nutrition to normal exerts a favorable influence on practically all disease conditions . . . Often the outcome will depend more upon the correction of the malnutrition than upon any therapy directed toward the malady."

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SQUIBB VITAMINS FOR THERAPY

now expanded to include additional essential vitamins—
and at no extra cost to your patients

Each Theragran Capsule supplies:

Vitamin A	25,000 U.S.P. units
Vitamin D	1,000 U.S.P. units
Thiamine Mononitrate	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Ascorbic Acid	200 mg.
Pyridoxine Hydrochloride	5 mg.
Calcium Pantothenate	20 mg.
Vitamin B_{12} Activity Concentrate	5 mcg.

Dosage: 1 or more capsules daily as indicated.

Supply: Family Packs of 180. Bottles of 30, 60, 100 and 1,000.

Also Available: THERAGRAN Liquid, bottles of 4 ounces; THERAGRAN Junior bottles of 30 and 100 capsules; and THERAGRAN-M (Squibb Vitamin-Minerals for Therapy), bottles of 30, 60, 100 and 1,000 capsule-shaped tablets.

References: 1. Tisdall, F. F.: Clinical Nutrition, ed. by Joliffe, N.; Tisdall, F. F., and Cannon, P. R.: Paul B. Hoeber, Inc., New York, 1950, p. 748. 2. Nutrition Reviews, *15*:47, (Feb.) 1957. 3. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, National Academy of Sciences and National Research Council, Washington, D. C., 1952, p. 18. 4. Halpern, S. L.: Ann. N. Y. Acad. Science *63*:147, (Oct. 28) 1955. 5. MacBryde, C. N.: Signs and Symptoms, J. B. Lippincott Co., Phila., 3rd Ed. 1957, p. 818.

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Squibb Quality—The Priceless Ingredient

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"...the most satisfactory form of treatment to date."[1]

Only 5 per cent of patients in severe coronary shock survive with conventional treatment. With Levophed 1 out of 3 patients will be saved.[2]

1. Briller, S. A.: *M. Clin. North America* 41:619, May, 1957.
2. Tainter, M. L.: *Bol. Asoc. méd. Puerto Rico* 47:305, Aug., 1955.

sixfold increase in survival rate with life-saving

Levophed®

bitartrate

natural antishock pressor hormone

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now, for the first time, **liquid** meprobamate

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Meprobamate, Wyeth

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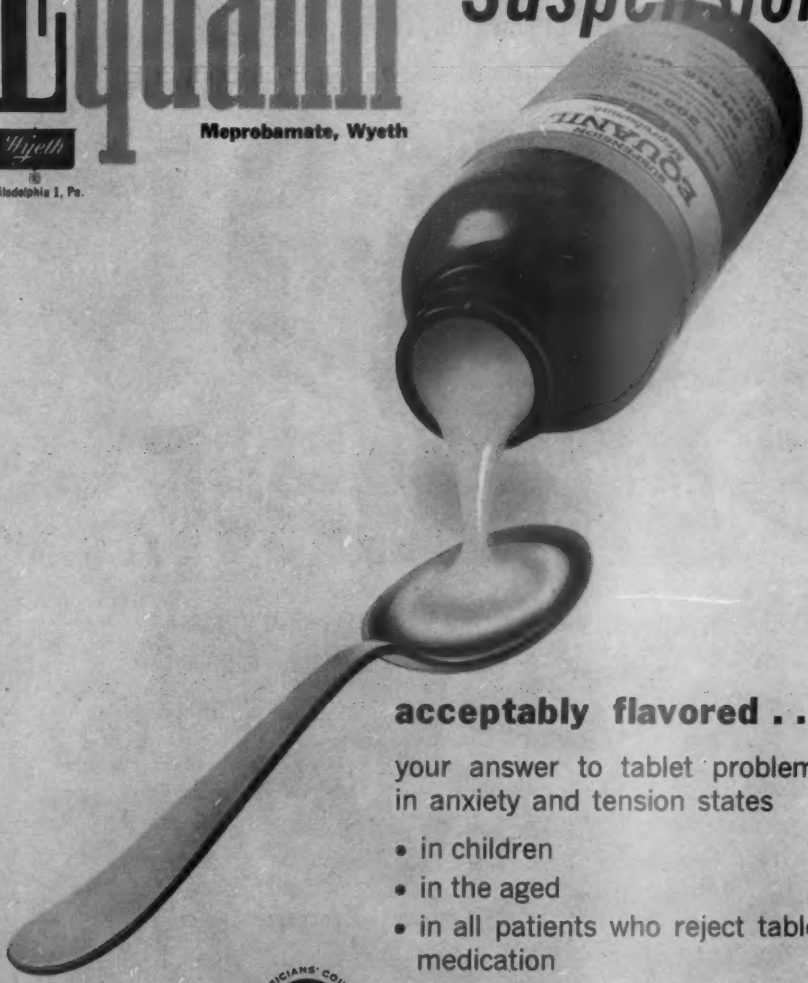

acceptably flavored . . .

your answer to tablet problems in anxiety and tension states

- in children
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SUPPLIED: Suspension, 200 mg. per 5-cc. teaspoonful, bottles of 4 fluidounces. Also available: Tablets, 400 mg., scored, bottles of 50; 200 mg., scored, vials of 50. WYSEALS® EQUANIL, tablets, 400 mg., vials of 50.

RELIEVES TENSION—MENTAL AND MUSCULAR

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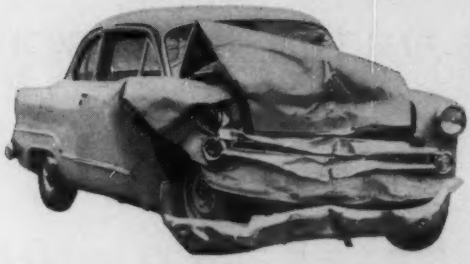

"...safety and practicality...recommend its use in the treatment of shock."[1]

SHOCK

INJECTION

ARAMINE®

BITARTRATE

(metaraminol bitartrate)

a superior vasopressor with a choice of routes for optimal response—no tissue slough observed[2-4]

ARAMINE rapidly raises and maintains blood pressure in shock. Simplicity of administration with reported freedom from tissue slough, necrosis or thrombophlebitis[1-4] encourages its prompt use. Patients respond with increased glomerular filtration rate, renal blood flow and urinary output. Vasopressor effect is smooth and sustained with no secondary fall in blood pressure and no tachyphylactic response to repeated injections.

Versatile ARAMINE is indicated in shock accompanying anaphylaxis, myocardial infarction, brain damage and infectious disease, as well as hypotension due to hemorrhage, surgery and other factors that lead to shock.

supplied: in 1-cc. ampuls and 10-cc. vials (10 mg. per cc.).

references: 1. Am. J. M. Sc. 230:357, Oct. 1955.
2. Circulation 16:1096, Dec. 1957.
3. Circulation 13:834, June 1956.
4. J.A.M.A. 163:1482, April 20, 1957.

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Now
in inflammatory anorectal disorders . . .

The Promise of Greater Relief

the first suppository to contain

hydrocortisone for effective control of proctitis

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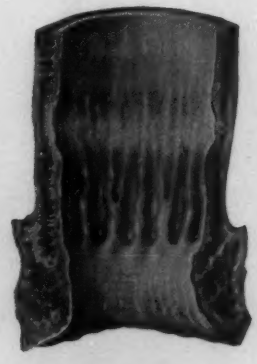

Postoperative Scar Tissue

Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

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THE HEART DISEASE PATIENT NEEDS RELIEF FROM EMOTIONAL STRESS

ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease."

(Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

TRANQUILIZATION WITH MILTOWN enhances recovery from acute cardiac episodes and makes patients more amenable to necessary limitations of activities.

(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

Miltown®

meprobamate (Wallace)

Available in 400 mg. scored and 200 mg. sugar-coated tablets. Also available as MEPROSPAN* (200 mg. meprobamate *continuous release* capsules). In combination with a nitrate, for angina pectoris: MILTRATE*—(Miltown 200 mg. + PETN 10 mg.). *TRADE-MARK CM-7720

Miltown causes no adverse effects on heart rate, blood pressure, respiration or other autonomic functions.

WALLACE LABORATORIES, *New Brunswick, N. J.*

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FOR PRACTICAL MANAGEMENT OF

HYPERTENSION

NEW

A SINGLE PROTOVERATRINE ALKALOID

potent . . . safe . . . and an important addition to "combination therapy"

The isolation of pure, crystalline protoveratrine A* makes available, for the first time, a single chemically standardized veratrum alkaloid. Now, blood pressure can be lowered with doses smaller than ever before possible in oral veratrum therapy.

In Protalba-R† Tablets, protoveratrine A (0.2 mg.) is combined with reserpine (0.08 mg.)—providing two effective hypotensive agents with constant, unvarying potency. In contrast to complex alkaloid mixtures which have uncertain activity, the effects of Protalba-R are predictable and reproducible.

Used alone, Protalba-R can produce a significant decrease in both systolic and diastolic pressure. And, it is the logical supplement to therapy when hypertension cannot be controlled by diet modification and psychogenic measures or the use of tranquilizers and diuretics.

protalba-R *Supplied in bottles of 100 cross-scored tablets.*

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Specifically Recommended in the Treatment of Prostatic Carcinoma

"ESTRADURIN"®

Brand of polyestradiol phosphate

Long-acting Estrogen with Unique Mode of Action

- simulates physiologic release of estrogen
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- maintains constant effective levels

"Estradurin" offers a safe, efficient, simple, and reliable means of insuring constant effective estrogen levels in patients with prostatic carcinoma.[1,2]

The unique mode of action is explained as follows:[3,4]

No depot effect at site of injection — Within 24 hours, 90 per cent of the total dose disappears from the injection site. Clearance from the blood stream is also rapid, and within 48 hours varying amounts appear in the reticuloendothelial cells where storage is apparently passive.

Hydrolysis in the blood stream — As the amount of circulating polyestradiol phosphate falls below a certain level, more passes from the reticuloendothelial system into the blood stream. Biologically active units of estradiol are slowly split off from the parent molecule. The free estradiol then exerts a normal estrogenic influence and is metabolized by the body in the same manner as the endogenous hormone.

Suggested Dosage: 40 mg. intramuscularly every two to four weeks or less frequently, depending on the clinical response of the patient. If the response is not satisfactory, doses up to 80 mg. may be used. Increasing the dose primarily prolongs the duration of action, but the amount of estrogen available at any one time is not significantly increased.

Availability: No. 451 — Each package provides: One "Secule"® containing 40 mg. polyestradiol phosphate and one 2 cc. ampul of sterile diluent.

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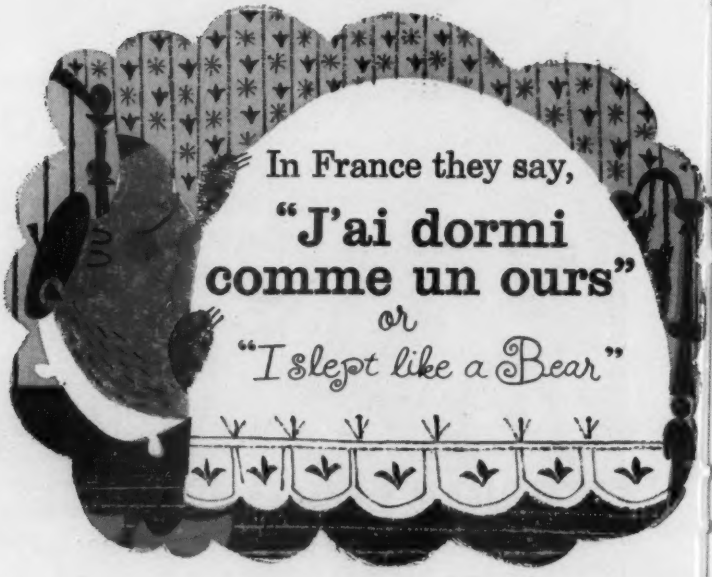

Your patients will say

"I slept like a log"

after taking NEW

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NOW in any language, NOLUDAR 300 is synonymous with sound, restful sleep.

EFFECTIVE: New NOLUDAR 300 acts promptly to induce sound, refreshing sleep of normal duration and quality[1,2,3] . . . followed by a clear-eyed awakening, without "hangover" effects.

SAFE: NOLUDAR 300 is free of barbiturate risks such as addiction or overdosage. Even minor side reactions are rare.[1,2,4] In terms of safety, NOLUDAR "appears to afford all one can possibly expect from a drug of this type."[1]

HIGHLY ACCEPTABLE: In a study of 1015 cases,[1] "all patients expressed satisfaction with the quality of action" of NOLUDAR. ". . . 97.9 per cent rated the hypnotic effect of NOLUDAR as at least equal, or superior to barbiturates they had previously received."

INDICATIONS: Insomnia due to mental unrest, excitement, fear, worry, apprehension or extreme fatigue.

DOSAGE: Adults—One 300-mg capsule before retiring. Do not exceed prescribed dosage.

REFERENCES:

1. O. Brandman, J, Coniaris and H. E. Keller, *J.M. Soc. New Jersey, 52*:246, 1955.
2. L. J. Cass, W. S. Frederik and J. B. Andosca, *New England J. Med., 253*:586, 1955.
3. E. H. Loughlin, W. G. Millin, J. Schwimmer and M. Schwimmer, *Internat. Rec. Med., 168*: 52, 1955.
4. P. A. Radnay, *Postgrad. Med., 21*:617, 1957.

NOLUDAR®—brand of methyprylon

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"Much better—thank you, doctor"

Proven in research

1. Highest tetracycline serum levels
2. Most consistently elevated serum levels
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Proven in practice

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CAPSULES ORAL SUSPENSION PEDIATRIC DROPS

THE *COSA*SAUR, emblem of the COSA antibiotics, symbolizes the natural origin of glucosamine—a substance widely distributed throughout the plant and animal world. Today, as in the dinosaur era, "Cosa" is basic to life.

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respiratory infections

prompt, high blood levels

consistently reliable and reproducible blood levels

minimal adverse reactions

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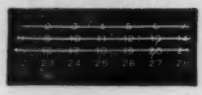

for PRURITUS ANI

orally treated with....Borcherdt

MALT SOUP EXTRACT

More and more physicians are telling us of the successful results from treating Pruritus Ani orally with Borcherdt's Malt Soup Extract. The intractable itching disappears in three or four days and the perianal skin becomes normal in three or four weeks. Even stubborn cases of many years standing usually yield or show marked improvement.

Malt Soup Extract is a non-diastatic barley malt extract neutralized with potassium carbonate. Most importantly, it promotes aciduric bacteria in the lower intestine, creates easily passed stools and overcomes, in a natural way, the alkaline condition so prevalent in cases of Pruritus Ani.

There are no side effects; no drug fastness, no gas pain. Malt Soup Extract is a food not a drug. Results are secured naturally and once attained medication can be discontinued or greatly reduced.

Malt Soup Extract is available in 8 and 16 ounce jars at most pharmacies coast to coast.

We will gladly send you samples and descriptive literature

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SERVING THE MEDICAL PROFESSION SINCE 1868

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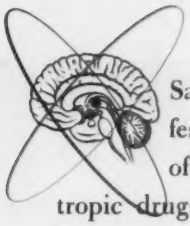

new concept

Satisfactory modification of the manifestations of abnormal brain activity is often achieved with individual psychotropic drugs acting on a single sector of the brain. In many patients, however, and despite high dosages, or change to another agent, response is only partial and is associated with lethargy and other more undesirable by-effects. Investigators have postulated that agents which will simultaneously alter the activity of more than one sector of the brain might produce a more satisfactory modification of undesirable emotional and behavioral patterns, thereby promoting a greatly improved total patient-response. To test this theory investigators recently have administered a low dosage of promazine, a phenothiazine, with a low dosage of meprobamate. The enhanced beneficial response elicited by this low-dosage dual attack is provided by PROZINE and warrants your consideration.

PROZINE

new agent

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meprobamate and promazine hydrochloride, Wyeth

SPECIFIC CONTROL THROUGH DUAL ACTION

PROZINE controls anxiety and tension as well as motor excitability. This effect on the components of emotional reaction is possible because of the dual sites of action of PROZINE—the thalamic and hypothalamic areas of the brain. The unique dual action of PROZINE enables the physician to exert more specific control of emotionally disturbed patients.

PROZINE is indicated in patients with a primary emotional disturbance, in patients with emotional disturbance unrelated to their organic disease, and in patients emotionally disturbed by primary organic disease.

PROZINE controls moderate to severe emotional disturbance manifested by apprehension and agitation, insomnia, depression, nausea and vomiting, gastrointestinal disturbances, alcoholism, menopausal symptoms, or premenstrual tension.

PROZINE in the recommended dosage (1 or 2 capsules, 3 or 4 times daily) produces more specific control than is obtainable with high doses of other ataractic agents. The benefits of a low-dosage regimen are unmistakable.

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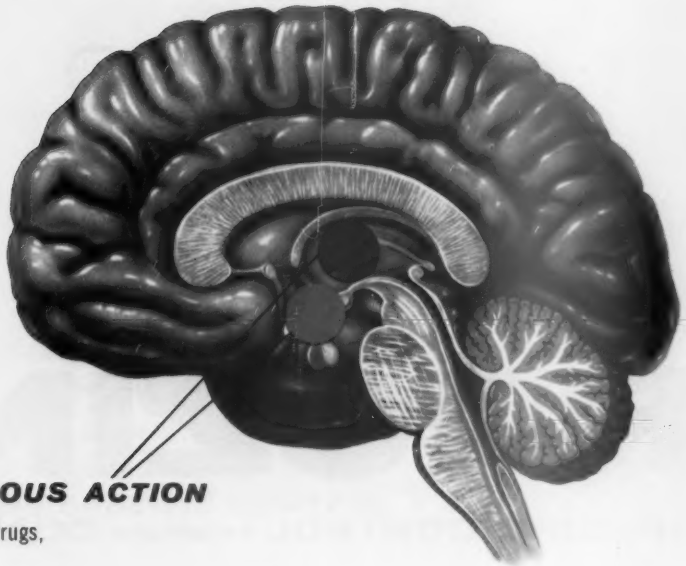
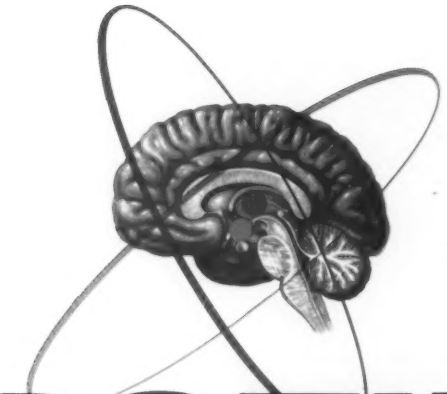


SIMULTANEOUS ACTION
of two psychotropic drugs,
affecting two areas
of the brain, produces
more ***SPECIFIC CONTROL***

thus ***in emotionally disturbed patients*** on **PROZINE** the dose required is diminished to the point where the incidence of side-effects and toxicity reactions is minimal and the patient is calm, tranquil, and amenable to additional therapy, whether it be educational, medical, or psychiatric.

PROZINE



PROZINE

SPECIFIC CONTROL THROUGH DUAL ACTION

The physician will see many applications for PROZINE in his day to day practice, particularly in overly apprehensive medical patients (including surgical and obstetrical cases) and in the management of emotional problems of children, adolescents and the aged; also in emotionally disturbed patients who receive little or no relief from analgesics, barbiturates, anticholinergics, antihypertensives, hormones (estrogens and corticoids). The dosages of these drugs may be dramatically reduced.

SUPPLIED: **PROZINE**—Bottles of 50 capsules. Each green and white capsule contains 200 mg. meprobamate and 25 mg. promazine hydrochloride.

Comprehensive literature is available

Wyeth®
Philadelphia 1, Pa.

PROOF OF

	PRIMARY E		
		Cap per	
	No.	1-3	
Anxiety Neurosis with Nausea, Vomiting, Fear, Tremor, Palpitations	74	37	
Anxiety Reaction with Headache or Migraine	20	10	
Anxiety Reaction causing Insomnia	24	16	
Apprehension and Tension	14	2	
Depression with Anxiety	30	15	
Psychoneurosis	32	7	
Pregnancy Nausea and Vomiting	53	51	
Preoperative Medication	7	7	
Alcoholism	66	7	5
Claustrophobia	3	1	
Hypochondriasis	1	1	-
Juvenile Delinquency	98	48	5
Total	422		

F OF CLINICAL EFFECTIVENESS—RESPONSE IN 972 PATIENTS† ON PROZINE

PRIMARY EMOTIONAL DISTURBANCE

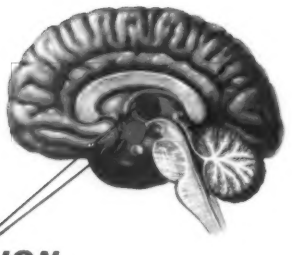
	No.	Capsules per Day 1-3	Capsules per Day 4-6	Duration of Treatment Days 1-7	Duration of Treatment Wks. 1-4	Duration of Treatment Mos. 1-6	Result IMPROVED	Result SAME	Result WORSE	SIDE EFFECT
r,	74	37	37	15	53	6	62	12	—	7
	20	10	10	3	15	2	16	4	—	1
	24	16	8	2	20	2	20	3	1	2
	14	2	12	1	9	4	12	2	—	—
	30	15	15	4	18	8	21	9	—	—
	32	7	25	9	18	5	25	6	1	4
	53	51	2	3	50	—	45	7	1	—
	7	7	—	7	—	—	7	—	—	—
	66	7	59	14	41	11	56	8	2	—
	3	1	2	1	2	—	3	—	—	—
	1	1	—	1	—	—	—	1	—	—
	98	48	50	—	—	98	82	16	—	—
	422									14

ORGANIC DISEASE WITH EMOTIONAL DISTURBANCE

	No.	Capsules per Day 1-3	Capsules per Day 4-6	Duration of Treatment Days 1-7	Duration of Treatment Wks. 1-4	Duration of Treatment Mos. 1-6	Result IMPROVED	Result SAME	Result WORSE	SIDE EFFECT
Gastrointestinal Peptic Ulcer Colitis Steatorrhea	48	26	22	5	24	19	41	7	—	1
Cardiovascular Hypertension Angina Pectoris	33	9	24	3	19	11	28	4	1	2
Dermatological Neurodermatitis Eczema Pruritus	34	2	32	3	27	4	21	9	4	6
Musculoskeletal Rheumatoid Arthritis Osteoarthritis Traumatic Arthritis Myositis	32	10	22	3	13	16	27	4	1	—
Endocrine Hyperthyroidism Hypothyroidism Diabetes Mellitus	11	5	6	1	6	4	10	1	—	—
Menopausal Syndrome	28	10	18	2	8	18	27	1	—	—
Allergic Hay Fever Asthma	15	12	3	9	4	2	7	6	2	2
Carcinoma	6	1	5	1	2	3	5	1	—	1
Chronic Brain Syndrome	19	15	4	—	9	10	14	5	—	—
Mentally Retarded (Disturbed)	96	54	42	—	—	96	84	11	1	1
Impotency	1	1	—	1	—	—	—	1	—	—
	323									13

PSYCHOTIC ILLNESS

	No.	Capsules per Day 1-3	Capsules per Day 4-6	Capsules per Day 7-10	Duration of Treatment Wks. 0-4	Duration of Treatment Months 1-3	Duration of Treatment Months 3-6	Symptomatic Response IMPROVED	Symptomatic Response SAME	Symptomatic Response WORSE	SIDE EFFECT
Postpartum Psychosis	2	1	—	1	1	1	—	1	1	—	—
Behavioral Problem (Psychotic)	5	3	2	—	3	2	—	4	1	—	—
Manic Depression	20	13	3	4	13	7	—	13	7	—	—
Schizophrenia Chronic Undifferentiated Hebephrenic Paranoid Catatonic Mixed	175	79	56	40	31	138	6	108	63	4	8
Involutional Psychosis	9	3	5	1	4	1	4	7	2	—	—
Phobic Reaction	6	2	4	—	5	1	—	3	3	—	—
Undifferentiated Psychosis	4	2	2	—	1	3	—	1	3	—	1
Obsessive Compulsive	2	—	2	—	2	—	—	1	1	—	—
Senile Psychosis	4	4	—	—	3	1	—	4	—	—	—
	227										9



SIMULTANEOUS ACTION
of two psychotropic drugs,
affecting two areas
of the brain, produces
more ***SPECIFIC CONTROL***

with minimal side-effects

IN 972 PATIENTS ON PROZINE—
patients with emotional disturbances, or with organic diseases and emotional disturbances, or with psychotic illnesses
INCIDENCE OF SIDE-EFFECTS WAS 3.7%

PROZINE

PROOF OF MINIMAL SID

ONLY 3.7% IN 972 PATIENT

	Anxiety Neurosis	Anxiety Reaction with Headache	Anxiety Reaction with Insomnia	Psycho-neurosis	Gastro-intestinal Disorders	Cardio-vascular Disease	Dermato-logical Disorders	Allergic Conditio
Fatigue Lethargy	5		1	1			1	
Confusion Euphoria							2	
Vertigo					1			
Epigastric Distention	1	1		2			1	
Burning in Throat							1	1
Nausea Vomiting			1					
Rash							1	
Flare-up Eczema								1
Dryness of Mouth	1					2		
Mild Hypotension								
Panic Reaction				1				

The occurrence of slight drowsiness in the first 48 hours of treatment indi
is in excess of the patient's requirements and is not regarded as a side-effec

†Data from 972 case reports on file at Wyeth Laboratories

PROZI

. SIDE-EFFECTS—

IENTS† ON PROZINE

Dermato-logical Disorders	Allergic Conditions	Carcinoma	Mentally Retarded	Schizo-phrenia	Undiffer-entiated Psychosis	Total Each Group
1		1				9
2						2
						1
1					1	6
1	1					2
				2		3
1			1	4		6
	1					1
						3
				2		2
						1
					Total	36

rs of treatment indicates the dose prescribed
rded as a side-effect of Prozine.

Incidence of Side-Effects 3.7%

ZINE

Wyeth®

Philadelphia 1, Pa.

to favor recovery in FIBROSIS...

Prescribe adequate daily amounts of

POTABA*

(Pure Potassium Aminobenzoate, Glenwood)

Institute treatment early and continue for a long enough period.

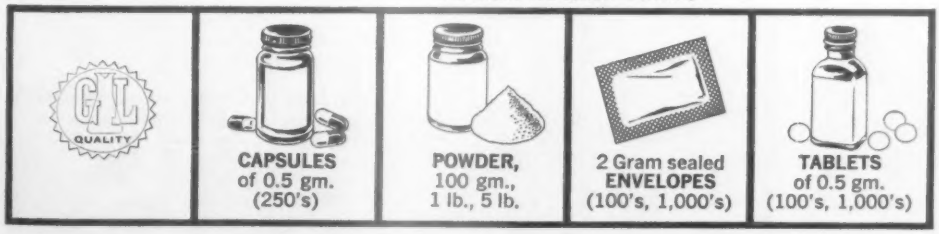
Evidence obtained from the observations of competent clinical investigators justifies the suggestion that this non-toxic drug may be found of great value wherever the pathological formation of fibrous tissue retards the patient's response to treatment.

Marked improvement in Scleroderma following treatment with POTABA prompted its use in *treatment resistant* Sarcoidosis and Peyronie's disease with the following recently reported results:

In 15 cases of Sarcoidosis cough, dyspnea and malaise decreased in 14. Partial or complete clearing of x-ray abnormalities was evident in 13 patients.[1]

21 Patients with Peyronie's disease receiving 12 gms. daily in divided doses for periods ranging from 3 months to 2 years responded as follows: Pain, where present disappeared from 16 of 16 cases. Penile deformity improved in 14 of 17 patients. Plaque decreased in 16 of 21.

POTABA DOSAGE FORMS



Complete literature available to physicians on request.
Also available: Information on PASKALIUM (Pure Potassium P.A.S.).
1., 2. To be published. *Trademarks of Glenwood Laboratories Inc.

GLENWOOD LABORATORIES INC. / BERGENFIELD, N. J.

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in management of the constipation "symptom-complex"

TWO NEW PRODUCTS

as convenient tablets . . . only 1 to 3 daily

for bulk

Celginace

Calcium and sodium alginates and dioctyl sodium sulfosuccinate, Mead Johnson

tablets granules

Celginace provides smooth, non-irritating, "hydrasorbent" bulk in the intestine, not in the stomach[1]...

this avoids excessive gastric fulness and depression of appetite.

1. Mulinos, M. G., and Glass, G. B. J.: Gastroenterology 24: 386-393 (May-Aug.) 1953.

AC-159 M

for stool softening—bulk —peristaltic stimulation

Combinace

Calcium and sodium alginates, dioctyl sodium sulfosuccinate and anthraquinone derivatives from cascara, Mead Johnson

tablets granules

When the patient presents a complex of symptoms and a comprehensive approach to therapy is indicated, Combinace provides (1) smooth, non-irritating, "hydrasorbent" bulk of alginates, (2) the predictable, yet gentle peristaltic stimulation of Peristim,®* (3) the moistening action of Colace.

A single product . . . with three-fold effect.

Mead Johnson
Symbol of service in medicine

the constipation "symptom-complex"

For each specific symptom or any combination of symptoms . . . you can select the anticonstipant which best meets *the needs of the individual patient:*

if the need is for	prescribe
softer, easier-to-pass stools	**Colace®****
predictable, gentle peristalsis	**Peri-Colace®†**
bulk in the intestine	**Calginace**
a combination of these effects	**Combinace**

*Standardized preparation of anthraquinone derivatives from cascara sagrada, Mead Johnson

**Dioctyl sodium sulfosuccinate, Mead Johnson

†Dioctyl sodium sulfosuccinate and anthraquinone derivatives from cascara, Mead Johnson

CLINICAL NOTES

HEMATOLOGY

A NEW INTRAVENOUS IRON COMPLEX

ASTRAFER® (ASTRA) I.V.

COMPOSITION A soluble, high-molecular, iron carbohydrate complex, equivalent to 20 mg. trivalent iron per cc., not to be confused with saccharated iron complexes.

PROPERTIES ASTRAFER® I.V. is a neutral solution and does not irritate the intima. It is relatively free from the side reactions previously encountered with other intravenous iron preparations. 70-100% of the iron supplied by this agent is utilized in hemoglobin synthesis. Patient improvement is marked by a measurable sense of well being, and is seen coincidentally with the return to normal of serum iron and hemoglobin levels, usually beginning with the third or fourth injection.

INDICATIONS Severe iron deficiency anemia characteristic of late pregnancy and massive or repeated blood loss, where rapid replenishment of large iron deficits is mandatory, and wherever orally administered iron may be either ineffective or poorly tolerated. To date, there is no evidence that this agent is of any value in anemias of polyarthritis or chronic nephritis. CONTRAINDICATIONS are pernicious anemia, leukemia or bone marrow depression, and liver damage.

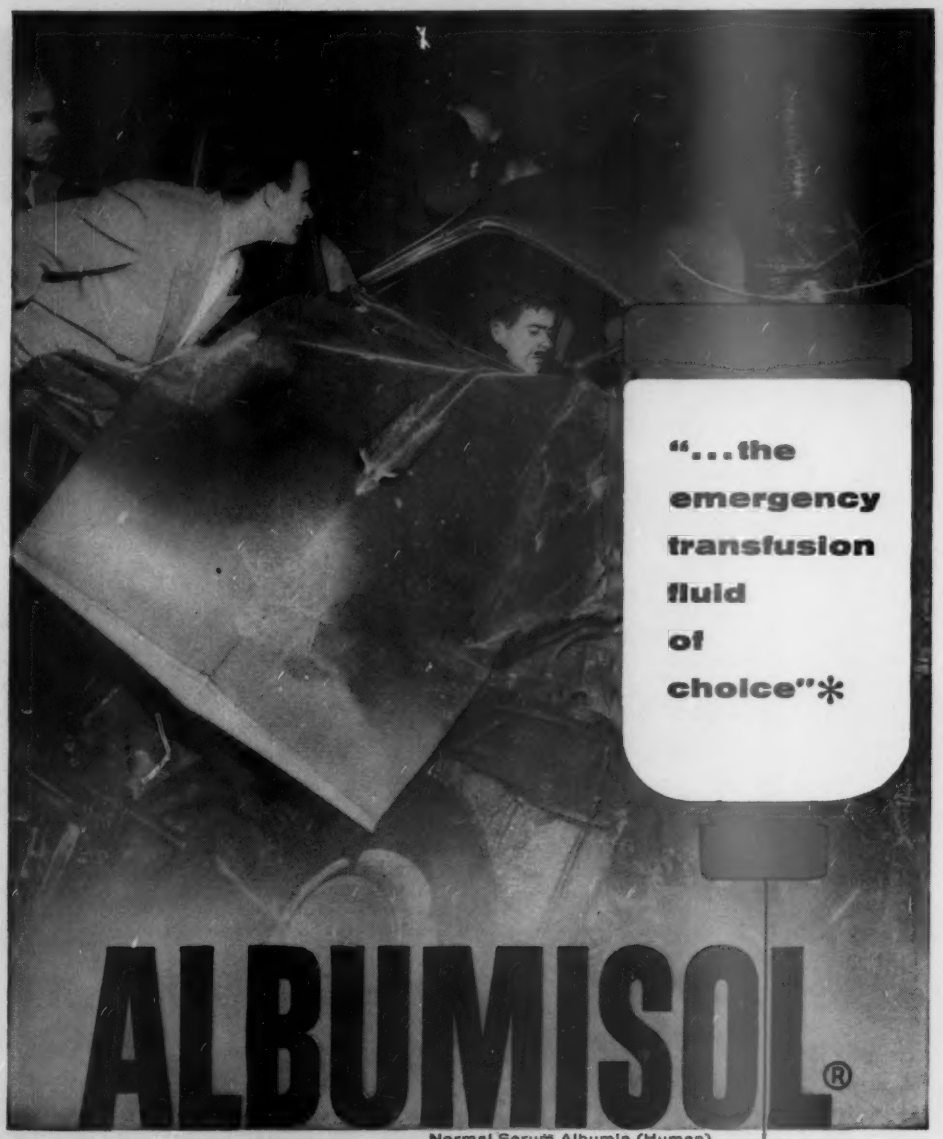
DOSAGE Initially, 1.5 cc. (30 mg.) to be administered slowly via the intravenous route. Patient should rest 15-30 minutes after each injection. Subsequent dosage increased according to instructions found in literature * accompanying each package.

SUPPLIED 5 cc. color-break ampules, boxes of 10

ASTRAFER® (ASTRA) I.V.

*Further information including clinical background and detailed dosage instructions available to physicians on request.

ASTRA PHARMACEUTICAL PRODUCTS, INC.
Worcester, Mass. U. S. A.



Normal Serum Albumin (Human)

No risk of serum hepatitis
Ready for administration; no storage problems
Human protein; readily metabolized
Contains no blood-clotting components
No grouping, typing, cross-matching required

Supplied: 'ALBUMISOL' 5%—in 250 and 500 cc. bottles in packages with a set of disposable intravenous equipment.

Also supplied: 'ALBUMISOL' 25% (Salt-Poor)—in 20 cc. bottles; in 50 cc. bottles in packages with a set of disposable intravenous equipment.

*Janeway, C.A.: Quart. Rev. Med. 9:153 (Aug.) 1952.

MSD

MERCK SHARP & DOHME
Division of MERCK & CO., Inc.
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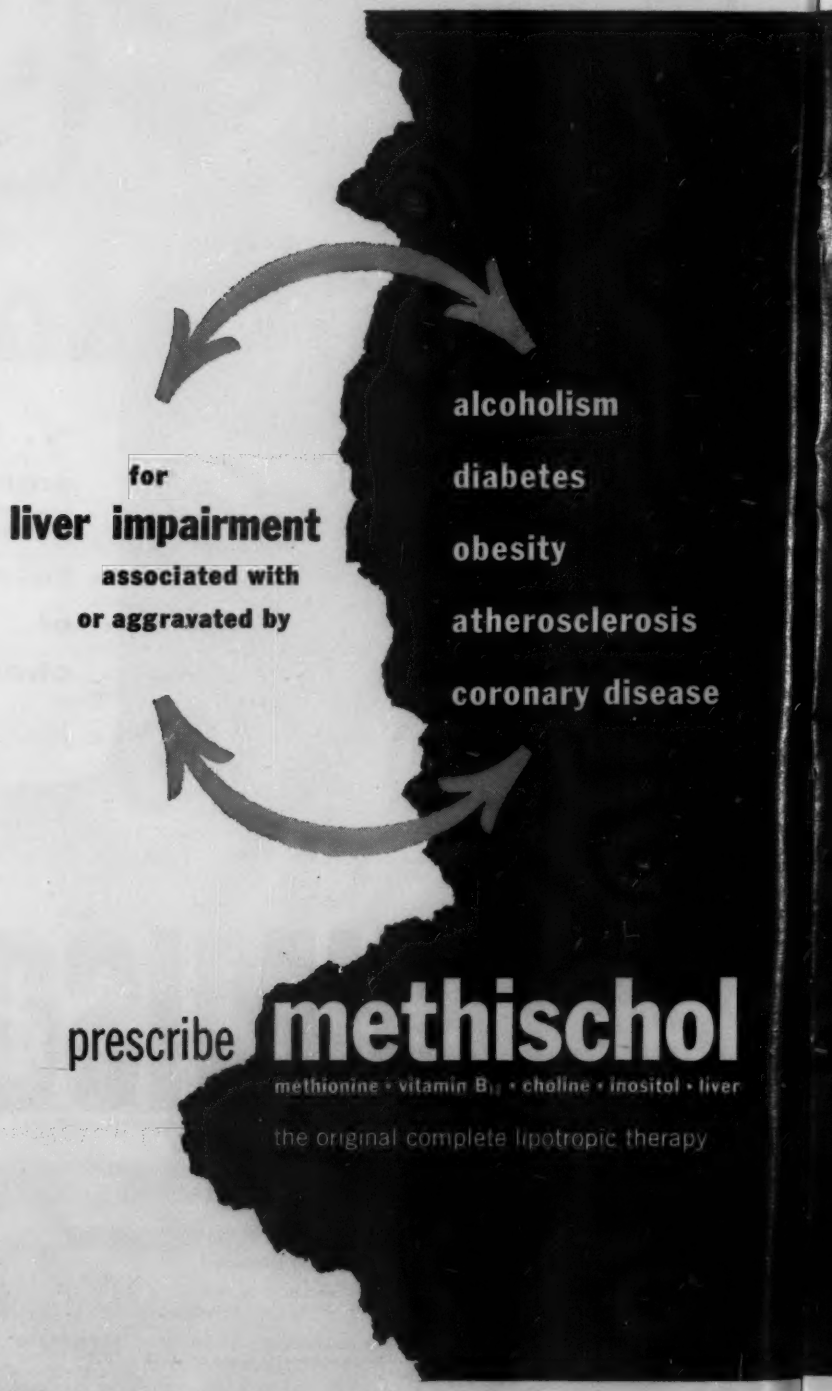

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fatty livers, portal cirrhosis, and widespread liver damage,
with failure in detoxifying ability, and general hepatic dysfunction are commonly encountered in diabetes, obesity, alcoholism, atherosclerosis and coronary disease.

conversely, certain of these conditions tend to cause exacerbation of the hepatic disturbance,
thus creating a vicious cycle seriously detrimental to the patient's health.

methischol helps terminate this vicious cycle
by increasing phospholipid turnover, reducing fatty deposits and fibrosis of the liver, stimulating regeneration of new liver cells, generally improving liver function.

when atherosclerosis and/or coronary disease occur
as they so frequently do in diabetes, alcoholism and obesity . . . Methischol aids in reducing elevated cholesterol levels, lowering chylomicron-lipomicron ratios towards the normal, and improving cholesterol and fat transport and metabolism.

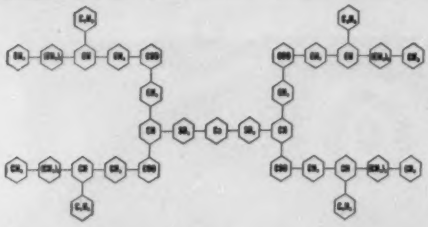
methischol

capsules bottles of 100, 250, 500 and 1000.
syrup bottles of 16 ounces and 1 gallon.

for samples and detailed literature write

u. s. vitamin corporation
(Arlington-Funk Laboratories, division)
250 East 43rd St., New York 17, N. Y.

NEW THERAPEUTIC CHEMICAL IN CONSTIPATION



Calcium Bis-(Dioctyl Sulfosuccinate)

The discovery by Wilson and Dickinson[1] at the University of Michigan that dioctyl sodium sulfosuccinate could correct constipation through fecal softening action marked a real advance in therapy. In cases of unimpaired bowel motility this new physico-chemical principle presented a new means of correcting bowel dysfunction without the need of catharsis.

Continuing research has now led to the development of a new therapeutic surfactant with more than double the surfactant effectiveness of the original dioctyl sodium sulfosuccinate.

This new substance, calcium bis-(dioctyl sulfosuccinate), reduces interfacial tension to a minimal value at a concentration of only 0.035 per cent. A minimal value of this order in dynes per centimeter requires 0.1 per cent or more of the older dioctyl sodium sulfosuccinate.

INTERFACIAL TENSION
(Oil-Water Interface)
Calcium Bis-(Dioctyl Sulfosuccinate)

Dynes/cm.	Concentration
55.0	0.00%
13.3	0.01%
9.9	0.02%
8.4	0.03%
7.4	0.035%

Improved homogenization of the immiscible lipoid and aqueous phases of the intestinal content depends upon maximum reduction of interfacial tension. The greatest degree of fecal softening is achieved with surfactant agents capable of reducing interfacial tension to minimal values. Calcium bis-(dioctyl sulfosuccinate) represents a markedly more effective surfactant agent since maximum surfactancy results from less than half the concentration of previously used surfactants.

DOSAGE:

DOXICAL 240 mg. SOFT GELATIN CAPSULES—*for adults, one daily.*

DOXICAL 50 mg. SOFT GELATIN CAPSULES—*for children and adults with minimum needs, one to three daily.*

1. Wilson, J. L., and Dickinson, D. G.: J.A.M.A. 158:261-263 (May 28) 1955.

This new chemical, definitely superior in surfactant action, is indicated in the treatment of chronic constipation where non-laxative fecal softening therapy is the preferred regimen.

The usual adult dose is 240 mg. daily. For children and adults with minimum needs, 50 to 150 mg. daily may be given.

DOXICAL

LLOYD BROTHERS, INC. CINCINNATI 3, OHIO

House call: agitation

The acutely excited patient can be quickly calmed when SPARINE is on hand in the physician's bag. In both medical and mental emergencies, SPARINE quiets hyperactivity, encourages cooperation, and simplifies difficult management.

SPARINE gives prompt control by parenteral injection and effective maintenance by the intramuscular or oral route. It is well tolerated.

Comprehensive literature supplied on request

Sparine® HYDROCHLORIDE

Promazine Hydrochloride, Wyeth

INJECTION TABLETS SYRUP

Wyeth®
Philadelphia 1, Pa.

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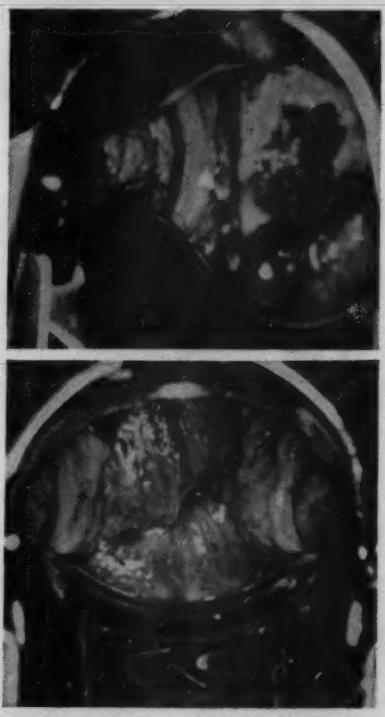

MONILIAL VAGINITIS

a common problem increasing year by year[1]

MYCOSTATIN

SQUIBB NYSTATIN

VAGINAL TABLETS specific / highly effective / safe

CANDIDIASIS is especially serious in diabetics . . . during pregnancy . . . in the debilitated . . . and when broad spectrum antibiotics have been administered in high dosage, with or without concurrent administration of cortisone or related steroids.

CLINICAL RESULTS. In 26 patients (11 pregnant) with vaginal moniliasis, treatment with Mycostatin Vaginal Tablets was completely successful in 92% of cases. Marked to moderate improvement was shown in the remainder.[2]

In a series of 59 patients with candidiasis (31 pregnant), intravaginal therapy with Mycostatin proved 100% successful in the pregnant patients; similar response was shown in 96.3% of the nonpregnant cases.[3]

SUPPLIED: Each Mycostatin Vaginal Tablet – individually foil wrapped contains Mycostatin, 100,000 units, and lactose, 0.93 Gm. Packages of 15 with applicator. Also available: Mycostatin Oral Tablets . . . Ointment . . . Dusting Powder . . . Powder for Suspension . . . Cream.

REFERENCES: 1. Lee, A.F., and Kelfer, W.S.: Northwest Med. 53:1227 (Dec.) 1954. • 2. Caruso, L.J.: New York J. Med. 58:1688 (May 15) 1958. • 3. Pace, H.R., and Schantz, S.I.: J.A.M.A. 162:268 (Sept. 22) 1956.

SQUIBB Squibb Quality – the Priceless Ingredient

'MYCOSTATIN' IS A SQUIBB TRADEMARK

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For Emotionally Disturbed Children

- whose intelligence is masked by behavior problems...
- who are unable to concentrate...
- whose attention span is too short...

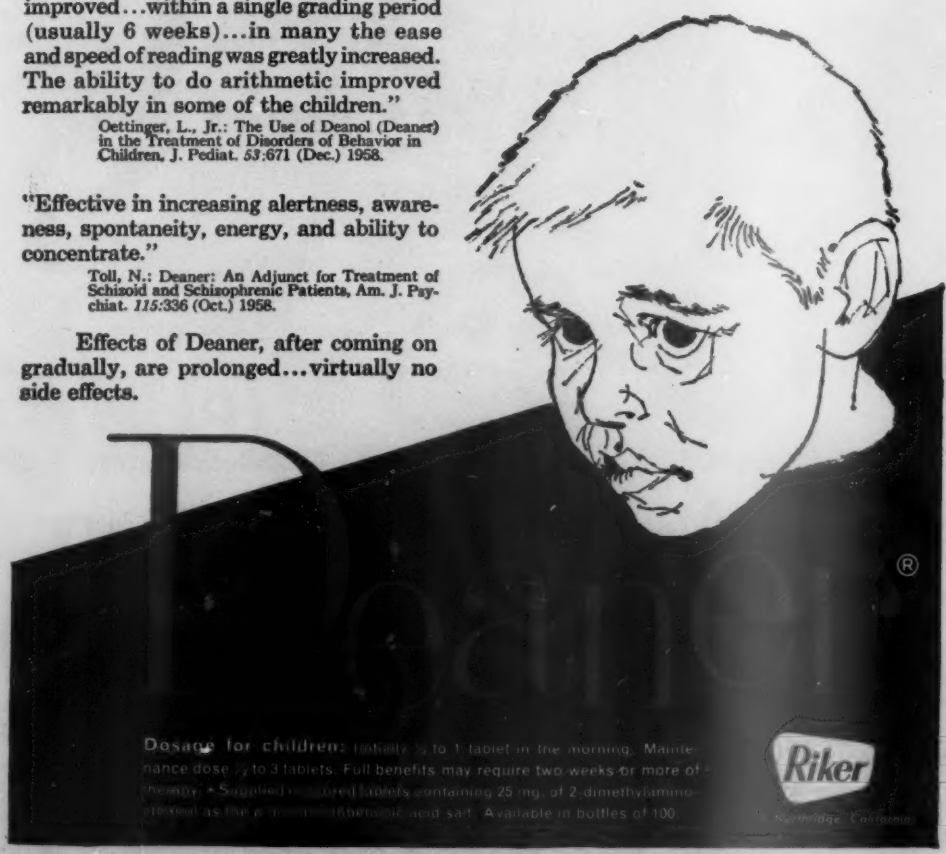
"Children came to act in more socially accepted patterns...learning in school improved...within a single grading period (usually 6 weeks)...in many the ease and speed of reading was greatly increased. The ability to do arithmetic improved remarkably in some of the children."

Oettinger, L., Jr.: The Use of Deanol (Deaner) in the Treatment of Disorders of Behavior in Children, J. Pediat. *53*:671 (Dec.) 1958.

"Effective in increasing alertness, awareness, spontaneity, energy, and ability to concentrate."

Toll, N.: Deaner: An Adjunct for Treatment of Schizoid and Schizophrenic Patients, Am. J. Psychiat. *115*:336 (Oct.) 1958.

Effects of Deaner, after coming on gradually, are prolonged...virtually no side effects.



Dosage for children: Initially ½ to 1 tablet in the morning. Maintenance dose ½ to 3 tablets. Full benefits may require two weeks or more of therapy. • Supplied as scored tablets containing 25 mg. of 2-dimethylaminoethanol as the p-acetamidobenzoic acid salt. Available in bottles of 100.

Riker

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the battle
won in the office
. . . is often lost in the stomach

Your ulcer and spastic-gut patients, who reflect their emotions in their stomachs, will more easily maintain "g.i. equilibrium" with the help of 'Combid' *Spansule* capsules.

'Combid' reduces
secretion
spasm
nausea and vomiting
anxiety, tension and stress

for 10 to 12 hours after just one dose.

Each capsule contains Compazine‡, 10 mg.; and Darbid§, S.K.F.'s *inherently long-acting* anticholinergic, 5 mg.

Combid* Spansule†
b.i.d.

Smith Kline & French Laboratories

★T.M. Reg. U.S. Pat. Off. †T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.
‡T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F.
§T.M. Reg. U.S. Pat. Off. for isopropamide, S.K.F.

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The whole family likes "Premarin"®

IN a sense, when you prescribe "Premarin" for a wife and mother who is suffering in the menopause, chances are you're treating the whole family. Junior, Sis, and Dad, just like Mom, can tell the difference right off.

Mother isn't just more tranquil on "Premarin" therapy. Hundreds of published reports tell us she takes a positive outlook on life. She feels *good*. And we all know that's the single most important factor for a happy home.

Women on "Premarin" receive treatment that covers every aspect of the menopause, including prompt relief of physical distress.

Is it any wonder physicians say the woman suffering in the menopause deserves "Premarin"? Many a family would agree.

"Premarin," conjugated estrogens (equine), a complete natural estrogen complex, is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N. Y.
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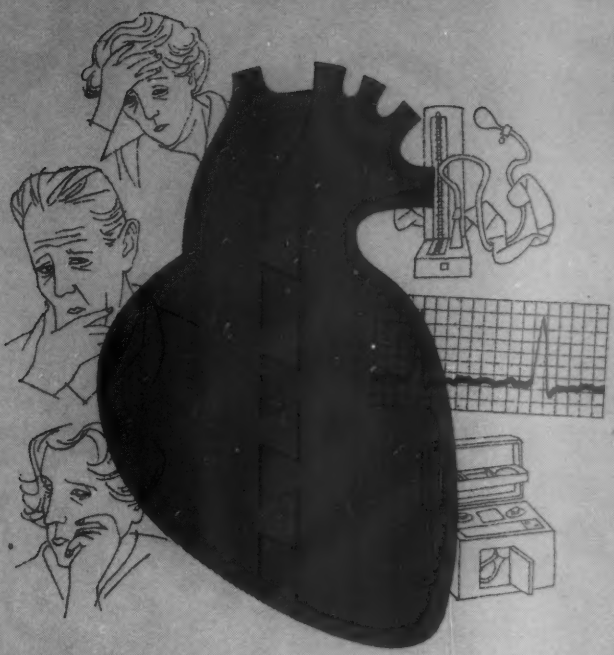
for prevention

of

angina attacks

more effective

than vasodilators alone



Miltrate*

MILTOWN® + PETN

The long-acting nitrate, PETN, helps maintain normal myocardial metabolism while Miltown relieves fear, anxiety and tension. As a result, Miltrate controls both physical and emotional causes of angina attacks.

Miltrate increases exercise tolerance

- reduces nitroglycerin dependence
- is notably safe for prolonged use
- provides convenient one-tablet dosage

Supplied: Bottles of 50 tablets.

Each tablet contains: 200 mg. Miltown + 10 mg. pentaerythritol tetranitrate.

Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime. Dosage should be individualized.

References:

1. Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders. Angiology 8:504, Dec. 1957.
2. Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.
3. Eskwith, I. S.: The holistic approach to angina pectoris. Am. Heart J. 55:621, April 1958.

WALLACE LABORATORIES, *New Brunswick, N. J.*

*TRADE-MARK

"early and marked regression"[1]

in acute superficial thrombophlebitis

BUTAZOLIDIN®

(phenylbutazone GEIGY)

nonhormonal anti-inflammatory agent

Relieves Pain Rapidly—BUTAZOLIDIN usually produces complete relief of pain within 24 hours or less.[1,2]

Resolves Inflammation—Fever subsides and local heat, tenderness and swelling regress quickly.[1,3,4] "In the majority of cases there was complete resolution by the fourth day."[5]

Permits Early Ambulation—"As a rule within 24 hours, most patients were able to get up and walk about...."[1] This rapid response to BUTAZOLIDIN greatly reduces disability and economic loss for patients.

Short Course of Treatment—Most patients require only from 2 to 7 days' therapy.[1,5]

BUTAZOLIDIN® (phenylbutazone GEIGY). Red coated tablets of 100 mg. BUTAZOLIDIN Alka Capsules, each containing BUTAZOLIDIN 100 mg.; aluminum hydroxide 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide 1.25 mg.

BUTAZOLIDIN being a potent therapeutic agent, physicians unfamiliar with it are urged to send for literature before instituting therapy.

GEIGY
Ardsley, New York

References: (1) Stein, I. D.: Circulation 12:833, 1955. (2) Potvin, L.: Bull. Assoc. méd. lang. franç. Canada 85:941, 1956. (3) Sigg, K.: Angiology 8:44, 1957. (4) Elder, H. H. A., and Armstrong, J. B.: Practitioner 178:479, 1957. (5) Broden, F. R.; Collins, C. G., and Sewell, J. W.: J. Louisiana M. Soc. 109:372, 1957.

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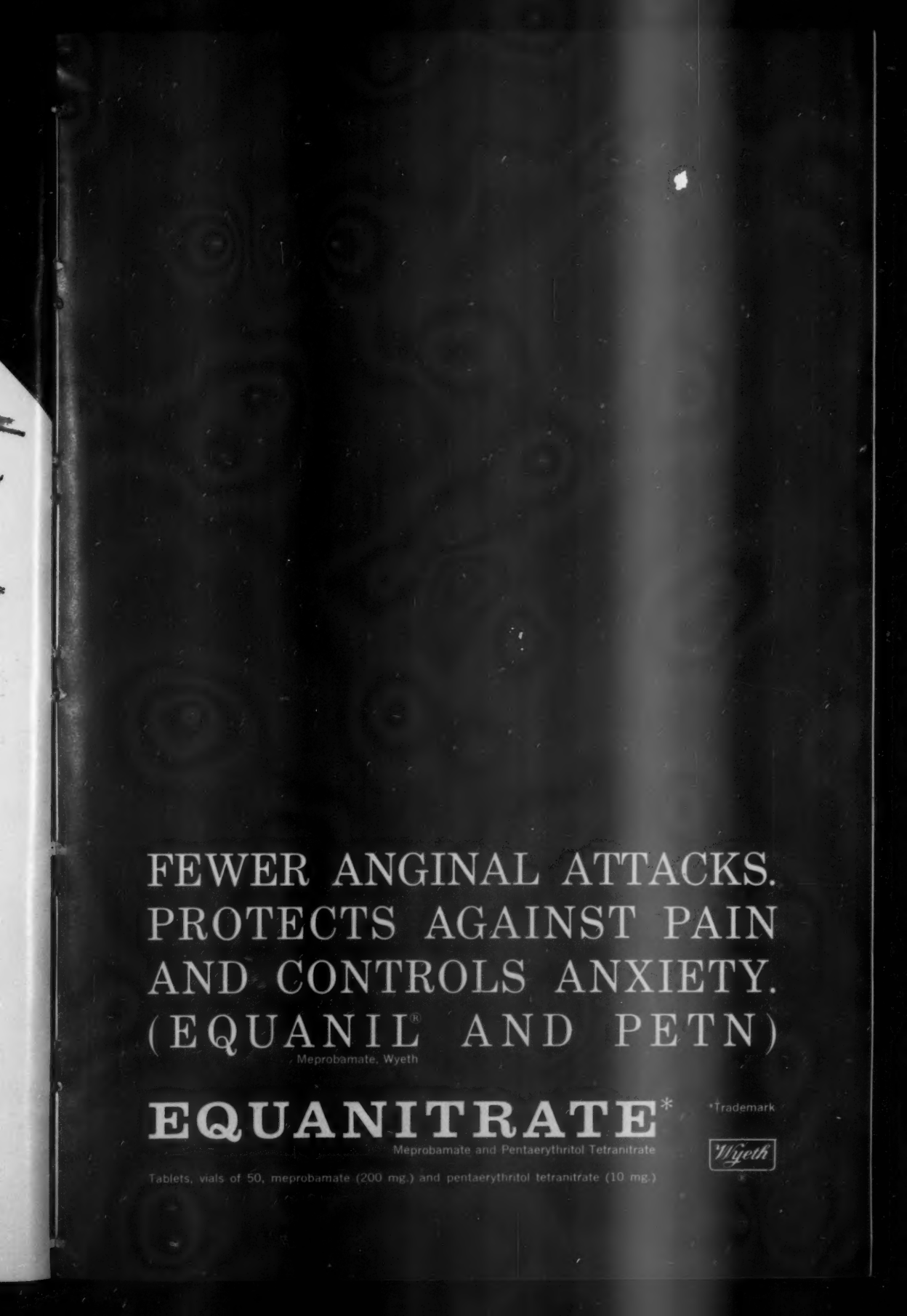
FEWER ANGINAL ATTACKS.
PROTECTS AGAINST PAIN
AND CONTROLS ANXIETY.
(EQUANIL® AND PETN)
Meprobamate, Wyeth
EQUANITRATE*
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Meprobamate and Pentaerythritol Tetranitrate
Wyeth
Tablets, vials of 50, meprobamate (200 mg.) and pentaerythritol tetranitrate (10 mg.)

the first bronchodilator

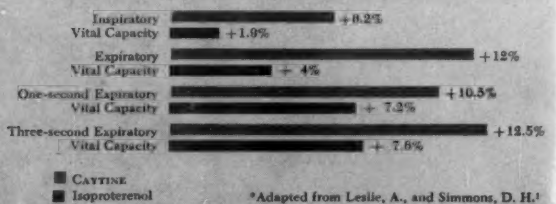
CAYTINE®

grip-breaker in bronchospasm

CAYTINE Tablets, Inhalation and Injection permit you to determine the treatment that gives the greatest relief with fewest side effects. CAYTINE increases vital capacity more than isoproterenol.[1] In geriatric patients CAYTINE "...was more effective than any previous medication used."[2] In a series of 126 patients, CAYTINE brought at least partial relief to 111 (88%).[3]

There are a few side effects, but no toxic reactions, with the use of CAYTINE. No elevation of blood pressure, no adverse ECG, EEG, hepatic, renal or hematologic changes have been noted. Patients may experience palpitations and anxiety and should be so warned.

Ventilometric Changes 5 Minutes after Equimolecular Doses of CAYTINE and Isoproterenol*



*Adapted from Leslie, A., and Simmons, D. H.[1]

clinically effective orally, parenterally, and by inhalation

asthma • emphysema

bronchitis • bronchiectasis

CAYTINE Tablets Plain, 2 mg., scored, bottles of 50; CAYTINE Tablets, 2 mg., with Pentobarbital, 32 mg. (warning: may be habit forming), scored, bottles of 50. CAYTINE Inhalation, 1:100, in 10 cc. bottles with dropper. CAYTINE Injection (intramuscular, subcutaneous), 0.5 mg./cc., in 1 cc. ampuls, boxes of 4.

CAYTINE is the *only* brand of α[(α-methyl-3,4-methylenedioxyphenethylamino)-methyl]-protocatechuyl alcohol hydrochloride.

(1) Leslie, A., and Simmons, D. H.: Am. J. M. Sc. *234*:321, 1957. (2) Settel, E.: Am. Pract. & Digest Treat. *8*:1249, 1957. (3) Itkin, I. H.; Burrage, W. S., and Irwin, J. W.: J. Allergy *27*:359, 1956.

For additional information request Brochure No. NDA 18, CAYTINE • Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin.

LAKESIDE

"... Well, I usually prescribe Rorer's Maalox. It's an excellent antacid, doesn't constipate and patients like its taste better."

MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel.
Suspension: Bottles of 12 fluidounces
Tablets: 0.4 Gram, Bottles of 100
Samples on request
WILLIAM H. RORER, INC., Philadelphia 44, Pennsylvania

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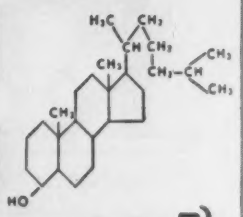
An effective key in reducing serum cholesterol...[1.]



RG®

LECITHIN

Natural-occurring [2.]

A complex of the highly refined soybean phosphatides derived wholly from soybeans.

A phospholipid [3.]

RG Lecithin facilitates the movement of fats through the body. It contains two highly active lipotropic agents: choline and inositol.

Essential fatty acids [2.]

RG Lecithin is rich in linoleic and linolenic acids.

Safe [4.]

No harmful side effects.

Palatable

Pleasant to take plain, or crumbled in juices or foods.

Economical and readily available in granular form, in 8-oz. and 1-lb. jars, or convenient 60-wafer package.

RG LECITHIN

For complete substantiating information write to Medical Consultant

Central Soya Company, Inc.
CHEMURGY DIVISION
1825 North Laramie Avenue Chicago 39, Illinois

1. Morrison, L. M., Serum Cholesterol Reduction with Lecithin; Geriatrics, 13:12 (Jan.) 1958. 2. Wittcoff, H., The Phosphatides; A.C.S. Monograph Series #112; Reinhold Pub. Corp. NYC 1951. 3. Bloor, W. R., Biochemistry of the Fatty Acids; A.C.S. Monograph Series #93, Reinhold Pub. Corp. NYC 1943. 4. Article, Lecithin in the Diet; Journal A.M.A. 168:1168 (Oct. 25) 1958.

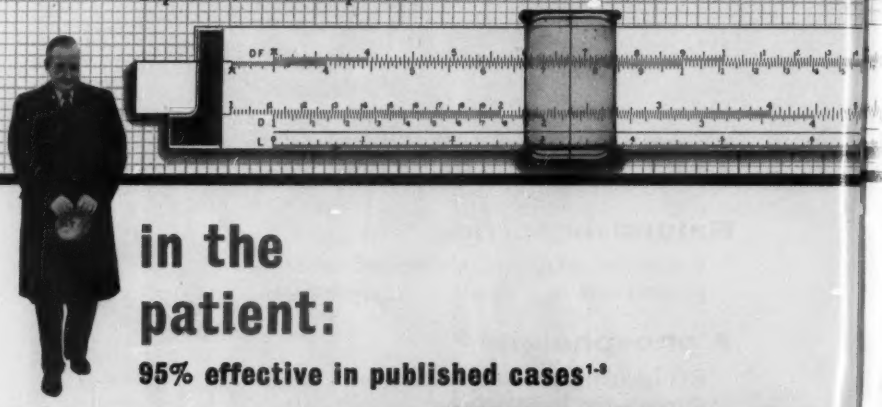
PRONOUNCED TAY-O

℞ Tao*

(triacetyloleandomycin)

Capsules / Oral Suspension

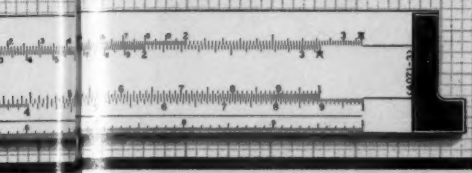
designed for superior control of common Gram-positive infections



in the patient:

95% effective in published cases[1-9]

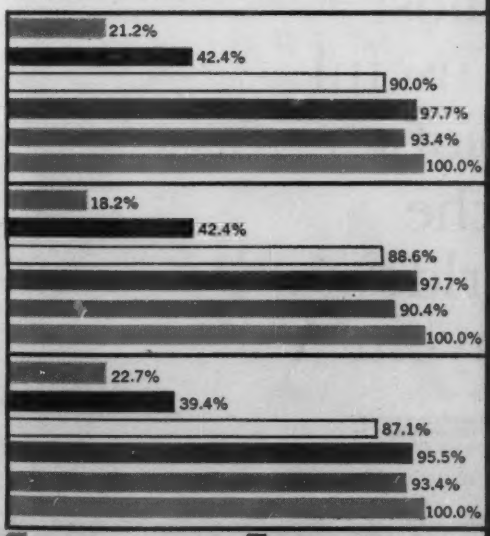
Conditions treated	No. of Patients	Cured	Improved	Failure
ALL INFECTIONS	558	448	80	30
Respiratory infections	258	208	31	19
Pharyngitis and/or tonsillitis	65	58	5	2
Pneumonia	90	66	17	7
Infectious asthma	44	38	—	6
Otitis media	31	29	2	—
Other respiratory (bronchitis, bronchiolitis, bronchiectasis, pneumonitis, laryngotracheitis, strep throat)	28	17	7	4
Skin and soft tissue infections	230	151	38	1
Infected wounds, incisions and lacerations	41	33	8	—
Abscesses	51	43	8	—
Furunculosis	58	51	6	1
Acne, pustular	43	28	15	—
Pyoderma	19	19	—	—
Other skin and soft tissue (infected burns, cellulitis, impetigo, ulcers, others)	18	17	1	—
Genitourinary infections	28	19	3	6
Acute pyelitis and cystitis	10	8	2	—
Urethritis with gonorrhea or cystitis	8	8	—	—
Pyelonephritis	4	1	—	3
Salpingitis	5	3	1	3
Pelvic inflammation with endometriosis	1	1	—	—
Miscellaneous (adenitis, enteritis, enterocolitis, subacute bacterial endocarditis, fever, hematoma, staphylococcus carriers, osteomyelitis, tenosynovitis, septic arthritis, acute bursitis, periarthritis)	42	30	8	4



in the laboratory:

over 90% effective against resistant staph

COMPARATIVE TESTS BY THREE METHODS (DISC, TUBE DILUTION, CYLINDER PLATE) ON 130 STAPHYLOCOCCI[9]



Percentage of organisms inhibited by the range of concentrations listed for each antibiotic.

Other Tao advantages:

Rapidly absorbed—stable in gastric acid,[7] TAO needs no retarding protective coating

Low in toxicity—freedom from side effects in 96% of patients treated; cessation of therapy is rarely required

Highly palatable—"practically tasteless"[7] active ingredient in a pleasant cherry-flavored medium.

Dosage and Administration: Dosage varies according to the severity of the infection. **For adults,** the average dose is 250 mg. q.i.d.; to 500 mg. q.i.d. in more severe infections. **For children** 8 months to 8 years, a daily dose of approximately 30 mg./Kg. body weight in divided doses has been found effective. Since TAO is therapeutically stable in gastric acid, it may be administered without regard to meals.

Supplied: TAO Capsules—250 mg. and 125 mg., bottles of 60. TAO for Oral Suspension—1.5 Gm., 125 mg. per teaspoonful (5 cc.) when reconstituted; unusually palatable cherry flavor; 2 oz. bottle.

References: 1. Koch, R., and Asay, L. D.: J. Pediat., in press. 2. Leming, B. H., Jr., et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 3. Mellman, et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 4. Olansky, S., and McCormick, G. E., Jr.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 5. Shubin, H., et al.: Antibiotics Annual 1957-1958, New York, N. Y., Medical Encyclopedia, Inc., 1958, p. 679. 6. Isenberg, H., and Karelitz, S.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 7. Wennersten, J. R.: Antibiotic Med. & Clin. Therapy 5:527 (Aug.) 1958. 8. Kaplan, M. A., and Goldin, M.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 9. Truant, J. P.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958.

TAO dosage forms— for specific clinical situations

TAO Pediatric Drops

For children—flavorful, easy to administer.

Supplied: When reconstituted, 100 mg. per cc. Special calibrated droppers—5 drops (approx. 25 mg.) and 10 drops (approx. 50 mg.). 10 cc. bottle.

TAO-AC (TAO analgesic, antihistaminic compound)

To eradicate pain and physical discomfort in respiratory disorders.

Supplied: In bottles of 36 capsules.

TAOMID® (TAO with triple sulfas)

For dual control of Gram-positive and Gram-negative infections.

Supplied: Tablets, bottles of 60. Oral Suspension, bottles of 60 cc.

Intramuscular or Intravenous

For direct action—in clinical emergencies.

Supplied: In 10 cc. vials.

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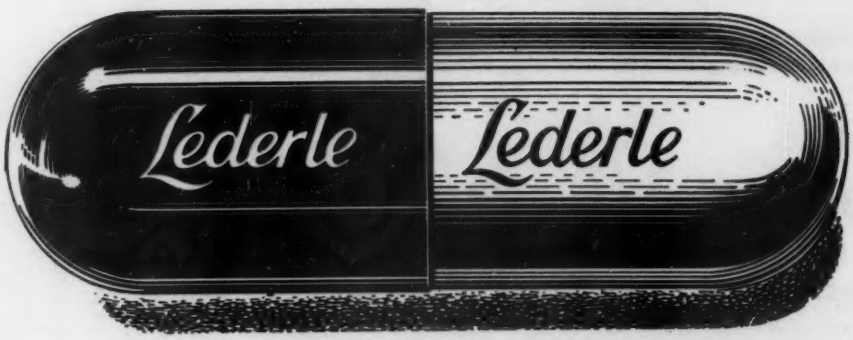
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

in
this capsule
lives the
most widely
used



the most
widely useful
antibiotic
in the
world
Achromycin® V

Tetracycline with
Citric Acid Lederle

SUPPLIED IN CAPSULES OF 250 MG.
WITH 250 MG. CITRIC ACID,
AND 100 MG. WITH 100 MG. CITRIC ACID.

Lederle LEDERLE LABORATORIES, A DIVISION OF AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

Amsterdam, Bernard: New York J. Med. 58:2199-2212 (July 1) 1958.

Panel Discussion on Proper Nutrition for the Older Age Group, J. Am. Geriatrics Soc. 6:787-802 (Nov.) 1958.

Leckert, J. T.; Donovan, C. B.; McHardy, G., and Cradic, H. E.: J. Louisiana M. Soc. *110*:260-266 (Aug.) 1958.

blood cholesterol regulation is worth while . . .

Arcofac lowers blood cholesterol levels. The Arcofac regimen is safe . . . well tolerated . . . effective . . . and imposes no radical changes in diet.

Arcofac supplies linoleic acid, an essential polyunsaturated fatty acid that lowers high blood cholesterol levels. It also provides vitamin B_6 which is deemed necessary to convert linoleic acid into the primary essential fatty acid, arachidonic acid. Vitamin E, a powerful antioxidant, helps maintain the fatty acid in an unsaturated state.

ARMOUR

Arcofac®

Armour Cholesterol Lowering Factor

Each tablespoonful of Arcofac contains:

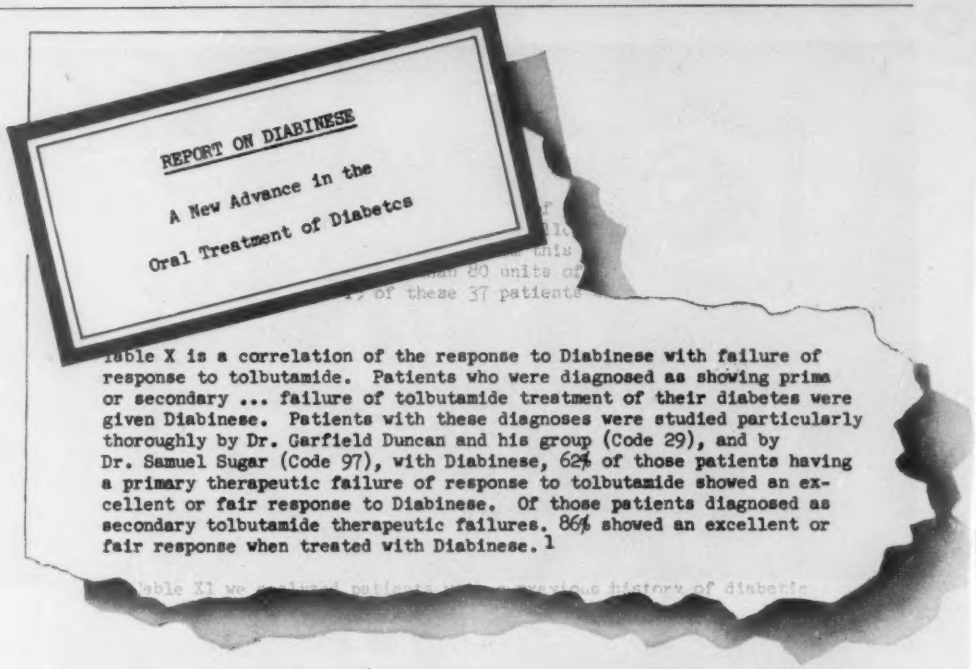
Essential fatty acids†.....6.8 Gm.
(measured as linoleic) with 2.5 I. U. of Vitamin E*

Pyridoxine hydrochloride.....1.0 mg.
(Vitamin B_6)

†Supplied by safflower oil which contains the highest concentration of polyunsaturated fatty acids of any commercially available vegetable oil.

*Added as mixed Tocopherols Concentrate, N.F.

ARMOUR PHARMACEUTICAL COMPANY • KANKAKEE, ILLINOIS / *A Leader in Biochemical Research*


REPORT ON DIABINESE
A New Advance in the
Oral Treatment of Diabetes
Table X is a correlation of the response to Diabinese with failure of response to tolbutamide. Patients who were diagnosed as showing prima or secondary ... failure of tolbutamide treatment of their diabetes were given Diabinese. Patients with these diagnoses were studied particularly thoroughly by Dr. Garfield Duncan and his group (Code 29), and by Dr. Samuel Sugar (Code 97), with Diabinese, 62% of those patients having a primary therapeutic failure of response to tolbutamide showed an excellent or fair response to Diabinese. Of those patients diagnosed as secondary tolbutamide therapeutic failures, 86% showed an excellent or fair response when treated with Diabinese.1

DIABINESE REDUCES PRIMARY AND SECONDARY FAILURES

REPORT ON DIABINESE
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Science for the world's well-being Pfizer

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc., Brooklyn 6, New York

1. *Summary of Diabinese Study Program.*

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An advance in potency of therapeutic activity

+

An advance in duration of therapeutic activity

▼

An advance in effectiveness over a wider range of patients

Diabinese exerts a hypoglycemic effect within one hour, which becomes maximal within three to six hours. It exhibits twice the potency of tolbutamide on acute administration and up to six times its potency on chronic administration. Most patients can be started on only 0.25 to 0.5 Gm. daily given as a single dose with breakfast.

Diabinese has a longer biologic half-life than tolbutamide. Excreted slowly, 80 to 90 per cent of one administration is eliminated in 96 hours. A single dose provides a therapeutic effect lasting 24 hours or longer. Since it remains in the blood as the active hypoglycemic material and is only gradually removed, Diabinese affords longer-lasting clinical benefit, with relatively constant blood levels, on *low, once-a-day dosage.*

The enhanced potency and duration of effectiveness of Diabinese is reflected in its notable record of clinical success in properly selected patients. Ninety-four per cent of *excellent* responses to Diabinese are in the most common group—the "maturity-onset" diabetics. Diabinese proved effective in 86.4 per cent of 1,675 patients over 40 years of age. Good results have even been obtained in some "brittle" diabetics, as well as in many patients exhibiting primary or secondary failure with tolbutamide.

Pfizer DIABINESE®

brand of chlorpropamide

once-a-day dosage

DOSAGE: IMPORTANT—Patients should not be given *starting* doses in excess of 0.5 Gm. daily. An initial dosage of 250 mg. daily is recommended for geriatric diabetics. For full details see Section 8 of Report on Diabinese.

SUPPLIED: 250 mg. tablets, scored; bottles of 60 and 250.
100 mg. tablets, scored; bottles of 100.

a MAJOR ADVANCE in the ORAL treatment of DIABETES

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A CIBA Documentary Report

How clinicians evaluate the safety and effectiveness of RITALIN® as a psychic stimulant

CONDITIONS TREATED	RESULTS	COMMENTS ON SAFETY
Depression accompanying chronic illness and convalescence from short-term illness; mild depression induced by life pressures; over-tranquilization.	"The drug gave a plateau type of stimulation, smooth onset, with no euphoria . . . The effect lasted about four hours, gave the patient a feeling of well-being . . ."	"The side effects of Ritalin are minimal." "The work showed that the drug had no effect on blood pressure, the blood count, urine or blood sugar, did not depress the appetite, and produced no tachycardia."[1]
Lethargy, fatigue and emotional depression secondary to chronic illness in elderly patients; mild depression secondary to short-term illness. (Twenty-three "normal," healthy people also received the drug.)	"For the entire 112 patients 66 per cent showed marked improvements [obvious drug effect and mood improvement] . . ."	"No serious side reactions were noted . . . In no case was it necessary to stop the drug. No evidence of significant effect upon blood pressure or pulse has been found. This is particularly interesting, since these side effects have been common with other mood elevating drugs . . ."[2]
Drug-induced psychophysiologic depression; physiologic after-effects of certain anesthetics; barbiturate intoxication; moribund states due to systemic infection. (All patients were epileptic, mentally retarded and/or brain damaged.)	"All except two [of 129] patients responded to the initial injection [of parenteral Ritalin] within 1½ to 15 minutes."	"In no instance was there any evidence of untoward effects." ". . . the very poor basic physical condition of our patients in this study, those associated with profound chronic brain damage, accentuates the safety of parenteral Ritalin . . ."[3]

DOSAGE: *Oral:* Dosage will depend upon indication and individual response. Many patients respond to 10 mg. b.i.d. or t.i.d. Others will require 20-mg. doses. In a few cases, 5-mg. doses will be adequate. If inability to sleep is encountered, last dose should be given before 6 p.m. *Parenteral:* 10 to 30 mg., intravenously or intramuscularly. RITALIN® hydrochloride (methylphenidate hydrochloride CIBA)

REFERENCES: 1. Natenshon, A. L.: Dis. Nerv. System *17*:392 (Dec.) 1956. 2. Landman, M. E., Preisig, R., and Perlman, M.: J. M. Soc. New Jersey *55*:55 (Feb.) 1958. 3. Carter, C. H., and Maley, M. C.: Dis. Nerv. System *18*:146 (April) 1957.

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SUMMIT, N. J.

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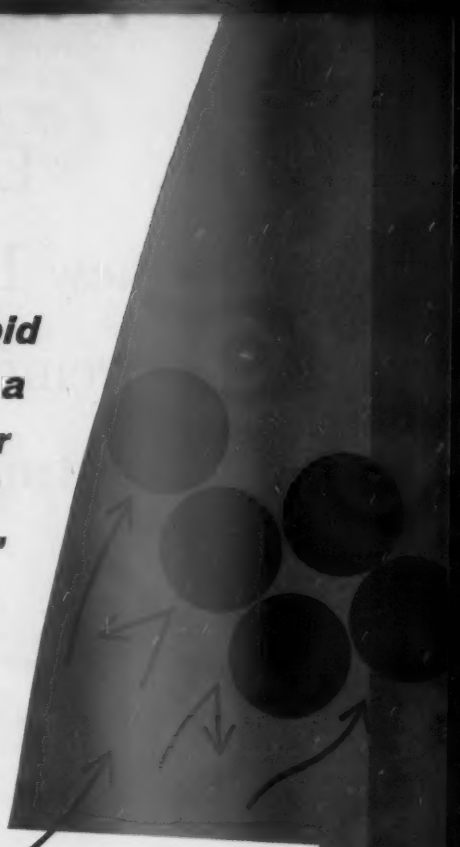

avoid a "winter of discontent" for congested noses by prescribing

METRETON NASAL SPRAY

"Meti" steroid-antihistaminic

the combined action of METICORTELONE® and CHLOR-TRIMETON® re-establishes nasal patency within minutes...for hours in acute coryza/nasopharyngitis/rhinitis/acute upper respiratory congestion/catarrhal disorders...safe for cardiac, hypertensive, pregnant and elderly patients...no sympathomimetic side effects

and for resistant allergies that defy ordinary therapy

METRETON TABLETS

"Meti" steroid-antihistaminic with ascorbic acid

supplied

METRETON® Nasal Spray, 15 cc. squeeze bottle

METRETON Tablets, bottles of 30 and 100

Meti,® brand of corticosteroids.

Each cc. of METRETON Nasal Spray contains 2 mg. (0.2%) prednisolone acetate and 3 mg. (0.3%) chlorprophenpyridamine gluconate. Each METRETON Tablet contains 2.5 mg. prednisone, 2 mg. chlorprophenpyridamine maleate and 75 mg. ascorbic acid.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

Schering

MT-J-119

Exactly <u>how</u> does new Halodrin* restore the "premenopausal prime" in postmenopausal women?

Webster defines "prime" as the period of greatest health, strength, and beauty. In a woman, these are the childbearing years between puberty and menopause—the years when her hormone production is highest.

The inevitable reduction in this hormone production as she enters the menopause often results in physical discomfort in the form of hot flushes, nervousness, insomnia, or a multiplicity of other symptoms with which you are familiar. Superimposed on this physical picture is the psychic trauma brought on by this unavoidable evidence of aging. The thing that brings her to a physician is simply that she "feels bad."

You can't make her 35 again—but the odds are good that you can make her feel like it! The secret is a combination of reassurance and hormones. The exact form and amount of the former defy objective analysis, but the latter can now be provided with scientific precision. Reduced to essentials, here is the explanation of exactly how hormones—in the form of Upjohn's new Halodrin—restore the "premenopausal prime."

The normal premenopausal woman secretes estrogens in the urine in the form of estradiol, estrone, and estriol, in an approximate 28-day average ratio of 39:15:46. Starting with this urinary excretion of estrogens, it is possible to calculate backwards and estimate the amount of estradiol that must have been secreted endogenously in order to produce these urinary levels. This is possible because the proportion of estrogens which appears in the urine following parenteral administration has been established in castrated women.

On this basis, the average endogenous output of estrogens is about 160 micrograms per day during a menstrual cycle, and 80 micrograms per day in postmenopausal women (see chart opposite). Therefore, the restoration of the "premenopausal prime" in the postmenopausal woman requires the replacement of approximately the equivalent of the 80 micrograms of estradiol per day that she no longer secretes endogenously.

Oral ethinyl estradiol is about 2 to 2½ times as potent as **parenteral** estradiol. Therefore, **the replacement of 80 micrograms of endogenous estradiol production per day is accomplished by the oral administration of 32 to 40 micrograms of ethinyl estradiol per day.**

Each Halodrin tablet contains 20 micrograms of ethinyl estradiol, which means that the recommended dosage of 2 tablets per day provides 40 micrograms of ethinyl estradiol. This offsets the loss of 80 micrograms of endogenous estradiol production in the menopausal woman; i.e., restores the "premenopausal prime."

Each Halodrin tablet also contains 1 mg. of Upjohn-developed Halotestin* (fluoxymesterone)—the most potent oral androgen known. The primary purpose is to "buffer" the ethinyl estradiol just enough to prevent breakthrough bleeding, which is obviously undesirable in the menopause. It also exerts other beneficial hormonal effects, one of which, in common with ethinyl estradiol, is a powerful anabolic action so desirable in patients of advanced years.

*TRADEMARK, REG. U. S. PAT. OFF. COPYRIGHT 1958, THE UPJOHN COMPANY

Upjohn

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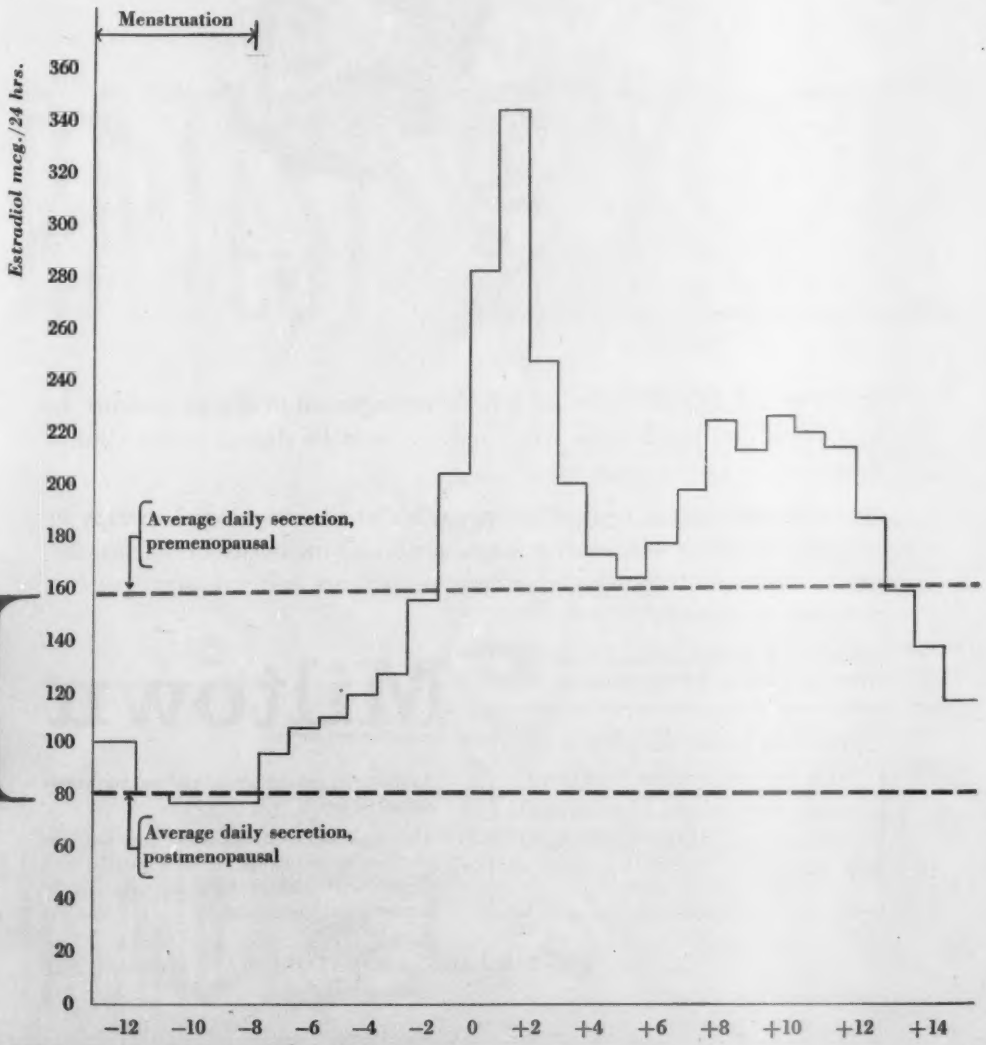
Endogenous estrogen secretion (mcg./24 hours)
(calculated from average 24-hour urinary excretion of estradiol, estrone, and estriol)



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RELIEVES NERVOUSNESS IN ALLERGIC PATIENTS

ANXIETY AND TENSION often complicate management of allergic patients. In such cases, the "psychogenic component . . . must be treated before clinical improvement can be expected."†

When tranquilization with Miltown was added to conventional therapy in asthma, allergic headache, hay fever, urticaria, angioneurotic edema and gastrointestinal allergy with emotional components, many resistant patients definitely improved.†

(†Eisenberg, B. C.: Role of tranquilizing drugs in allergy. J.A.M.A. **163**:934, March 16, 1957.)

Miltown causes no adverse effects on respiratory functions, nasal secretions, intestinal motility, or other autonomic functions.

Miltown®
meprobamate (Wallace)

Available in 400 mg. scored and 200 mg. sugar-coated tablets.

Also available as MEPROSPAN® (200 mg. meprobamate *continuous release* capsules) and MEPROTABS® (unidentifiable 400 mg. meprobamate sugar-coated tablets). ®TRADE-MARK

CM-7706

WALLACE LABORATORIES, *New Brunswick, N. J.*

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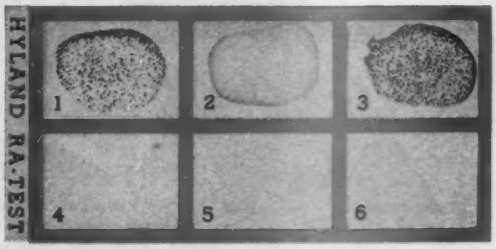
NEW...HYLAND RA-TEST A FAST, SIMPLE, RELIABLE SCREENING TEST FOR RHEUMATOID ARTHRITIS

a rapid slide modification of the latex fixation test

RA-TEST*



EASY TO PERFORM—just mix separate drops of Latex-Globulin Reagent with: (1) patient's diluted serum, (2) Negative Control Serum, and (3) Positive Control Serum on divided areas of slide.

EASY TO READ—positive reactions (indicating presence of rheumatoid factor) are clearly visible to the naked eye in a few seconds. Negative tests remain smooth, with no visible clumping.

SUPPLIED—in compact kits containing 5 cc. Latex-Globulin Reagent, 2 cc. Positive Control Serum, 2 cc. Negative Control Serum, 100 cc. Glycine-Saline Buffer Diluent, and divided glass slide. Each kit sufficient for at least 100 tests. Test components are also available separately.

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HYLAND Hyland

*Trade Mark of Hyland Laboratories

in peptic ulcer

REFRACTORY CASES RESPOND TO

NEW

DARICON* *tablets*

OXYPHENCYCLIMINE HYDROCHLORIDE

POTENT ANTICHOLINERGIC ACTION

curbs secretion when excessive
normalizes motility when overactive

Activity appears to be restricted to the desired site of action. Predictable therapeutic response in refractory cases.

Potency and Prolonged Duration of Action
10 mg. b.i.d. Average Dose • Supplied as:
10 mg. white, scored tablets

References: 1. Finkelstein, Murray: Journal of Pharmacology and Experimental Therapeutics, in press. 2. Winkelstein, Asher: Paper in preparation.

*Trademark

Pfizer *Science for the world's well-being*

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REFRACTORY CASES RESPOND

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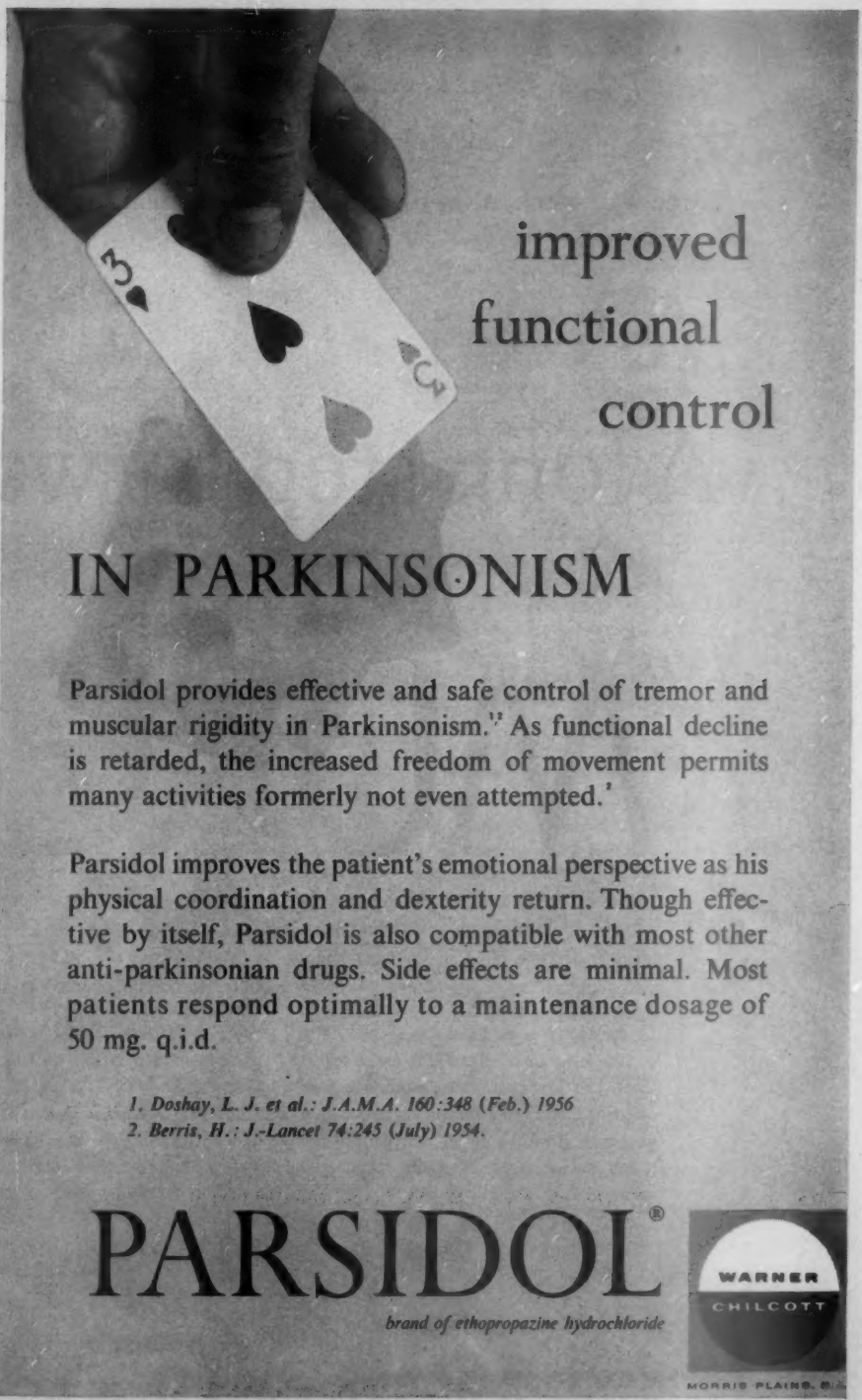
improved
functional
control
IN PARKINSONISM
Parsidol provides effective and safe control of tremor and muscular rigidity in Parkinsonism.[1,2] As functional decline is retarded, the increased freedom of movement permits many activities formerly not even attempted.[2]
Parsidol improves the patient's emotional perspective as his physical coordination and dexterity return. Though effective by itself, Parsidol is also compatible with most other anti-parkinsonian drugs. Side effects are minimal. Most patients respond optimally to a maintenance dosage of 50 mg. q.i.d.
1. Doshay, L. J. et al.: J.A.M.A. 160:348 (Feb.) 1956
2. Berris, H.: J.-Lancet 74:245 (July) 1954.
PARSIDOL®
brand of ethopropazine hydrochloride
WARNER
CHILCOTT
MORRIS PLAINS, N. J.

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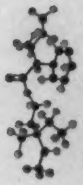
three-way mechanism of action  in one molecule

A long step forward

"MUREL"®

Brand of Valethamate bromide

"MUREL" is the newest development of research in quaternary ammonium compounds. It advances today's therapy of G.U., G.I. and biliary tract spasm toward the ideal in decisive relief without intolerance or drug-induced complications. "MUREL" also supplements peptic ulcer therapy by breaking the chain reaction of spasm-pain.

Dosage: Mild to moderate cases: initially, 1 or 2 tablets four times daily. Acute or severe cases: 1 to 2 cc. (10-20 mg.) intravenously or intramuscularly every four to six hours up to maximum of 60 mg. in 24 hour period. The higher dosage range is usually required in spasm of G.U. and biliary tract.

Supplied: "MUREL" Tablets—10 mg. Valethamate bromide, bottles of 100 and 1,000. "MUREL" Injectable—10 mg. per cc., vials of 5 cc. (Also available: "MUREL" with Phenobarbital Tablets—10 mg. Valethamate bromide with ¼ gr. phenobarbital per tablet, bottles of 100 and 1,000.)

Ayerst Laboratories • New York 16, N. Y. • Montreal, Canada

Ayerst

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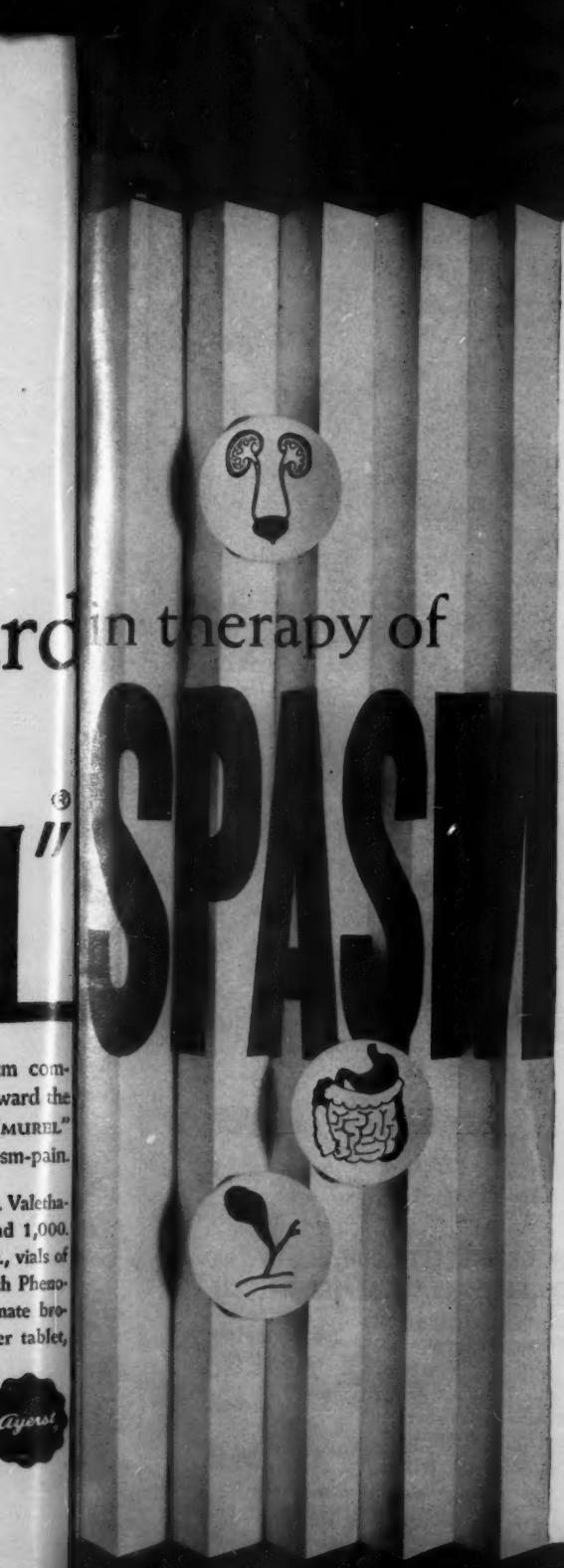
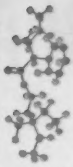




Three-Way Mechanism of Action in One Molecule

"MUREL" unites three mechanisms specific for smooth muscle spasmolysis: (1) anticholinergic inhibition of parasympathetic transmission, (2) musculotropic action with specific affinity for smooth muscle fibers, and (3) ganglionic blocking action at the synaptic level.

Precludes or Minimizes Untoward Side Effects

"MUREL" is especially well tolerated because: (1) coordination of the three component actions permits significantly low dosages and also reduces reaction potential of any one mechanism, (2) a natural specificity confines the anticholinergic action to the effector cells of smooth muscle, (3) definite but transient ganglionic blocking action eliminates undesirable parasympathetic disturbances, (4) rapid detoxification and excretion prevent cumulative effect.

Widely Useful— Clinically Demonstrated

"MUREL" extends the clinical scope of dependable spasmolytic therapy, with indications ranging from mild to severe hypertonicity. In postoperative *genitourinary* spasm, cystitis and pyelitis—effective relief of pain and spasm was noted in all of 75 patients.[1] In *peptic ulcer*—complete or substantial relief from the pain/spasm cycle was reported in 119 out of 127 patients.[2,3] In *biliary spasm* and chronic cholecystopathies with or without stones—prompt, complete control of spasm was obtained in 20 out of 22 patients.[3]

Peiser[2] states that even extremely strong convulsive abdominal pain and violent vomiting could be eliminated or substantially improved, and no unpleasant side effects or toxic reactions were noted at any time.

1. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.
2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955.
3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955.

AN AMES CLINIQUICK™

CLINICAL BRIEFS FROM MODERN PRACTICE

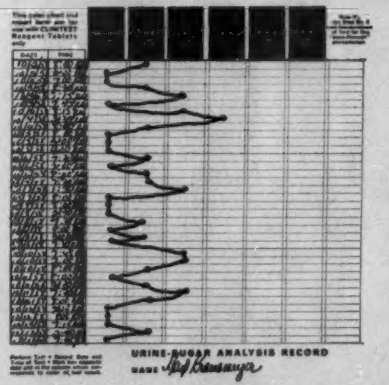
What differentiates "renal diabetes" (renal glycosuria) from diabetes mellitus?

Blood sugar levels. In renal glycosuria they are normal; in untreated diabetes, fasting blood sugars are usually 130 mg.% or over and postprandial levels 170 mg.%, or more.

Source: Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, Lea & Febiger, 1952, pp. 701-702.

A "URINE-SUGAR PROFILE" FOR CLOSER CONTROL

The new CLINITEST Urine-Sugar Analysis Set contains an improved Analysis Record form that enables even closer control of the *moderate* and the *severe* diabetic. Daily urine-sugar readings may be connected to produce a graph—a day-to-day "profile" that reveals at a glance individual trends and degree of control.



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CLINITEST®

BRAND

FOR EVEN BETTER CONTROL OF THE MODERATE AND THE SEVERE DIABETIC

the STANDARDIZED urine-sugar test for reliable quantitative estimations "...the most satisfactory method for home and office routine testing."*

*GP *16*:121 (August) 1957.

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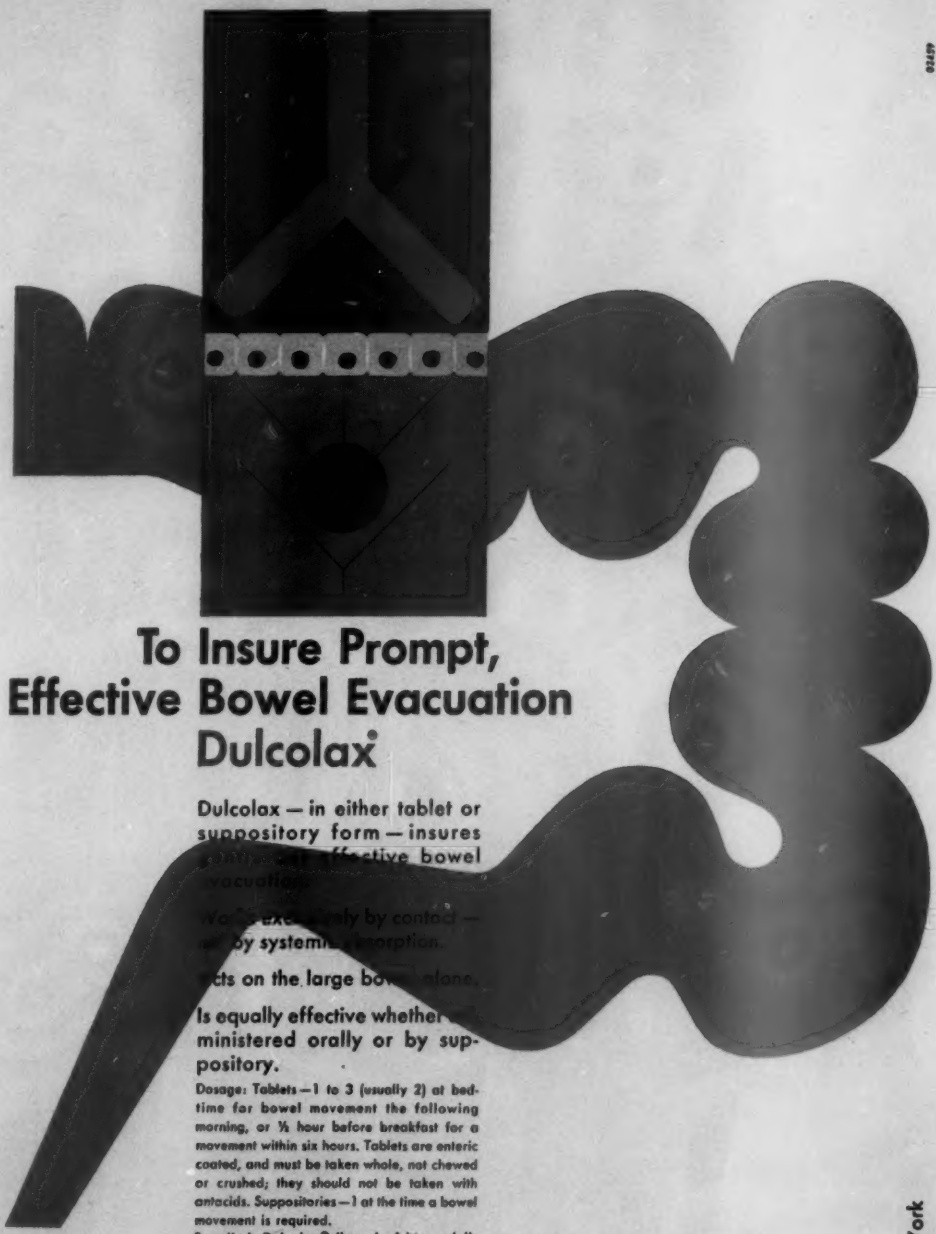

To Insure Prompt, Effective Bowel Evacuation

Dulcolax®

Dulcolax — in either tablet or suppository form — insures [illegible] effective bowel evacuation.

[illegible] only by contact — [illegible] by systemic absorption.

[illegible]cts on the large bo[illegible] alone.

Is equally effective whether [illegible] ministered orally or by suppository.

Dosage: Tablets—1 to 3 (usually 2) at bedtime for bowel movement the following morning, or ½ hour before breakfast for a movement within six hours. Tablets are enteric coated, and must be taken whole, not chewed or crushed; they should not be taken with antacids. Suppositories—1 at the time a bowel movement is required.

Supplied: Dulcolax® (brand of bisacodyl). Yellow enteric-coated tablets of 5 mg. in boxes of 6 and bottles of 100. Suppositories of 10 mg. in boxes of 6. Under license from C. H. Boehringer Sohn, Ingelheim.

Contact Laxative

Geigy

Ardsley, New York

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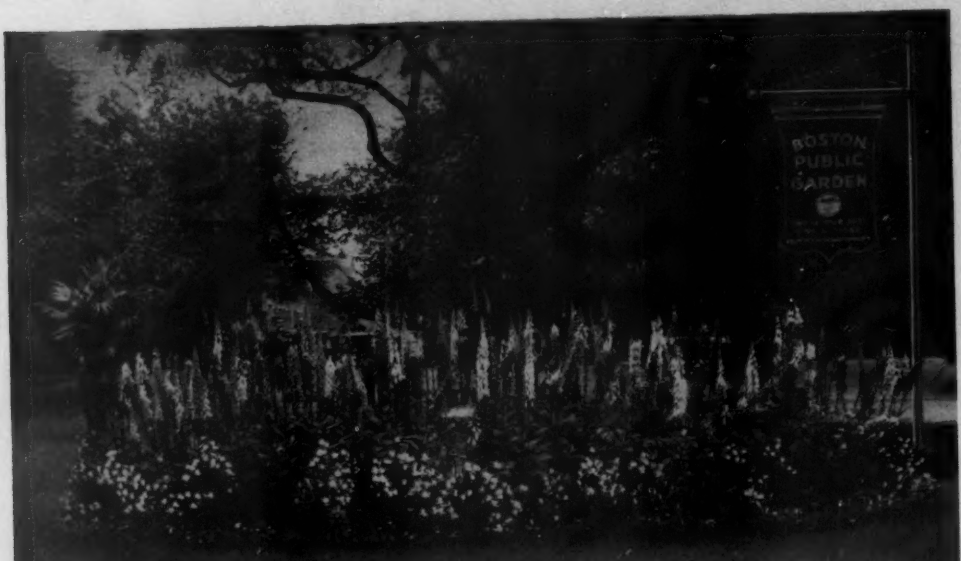
Tetracycline with Citric Acid Lederle

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York



Bed of Digitalis purpurea
with Campanula (Canterbury Bells) in foreground

Not far from here are manufactured
from the powdered leaf
Pil. Digitalis (Davies, Rose)
0.1 Gram (1½ grains) or 1 U.S.P. Digitalis Unit.
They are physiologically standardized,
with an expiration date on each package.
Being Digitalis in its completeness,
this preparation comprises the
entire therapeutic value of the drug.
It provides the physician with a safe and effective
means of digitalizing the cardiac patient
and of maintaining the necessary saturation.
Security lies in prescribing the
"original bottle of 35 pills, Davies, Rose."

Clinical samples and literature sent to physicians on request

Davies, Rose & Co., Ltd. Boston 18, Mass.

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HOW TO HELP TIME MARCH A LITTLE MORE MERRILY

Time's relentless march is often accompanied by certain degenerative changes.

In some cases, the onset of these changes can be postponed, or their progress can be slowed by proper dietary management. The inclusion of PET *Instant* Nonfat Dry Milk can frequently prove helpful.

PET *Instant* is 36.5% milk protein in its dry form. It can, therefore, supply important quantities of high-quality usable protein in concentrated form when diminishing appetites result in decreased intake of this essential food element.

In other instances, the fact that new PET *Instant* is virtually fat-free makes it particularly suitable for the lessened calorie requirements of oldsters.

Reconstituted, new PET *Instant* is refreshing as well as wholesome . . . highly palatable as a beverage, or as an ingredient in prepared dishes.

Nourishing, convenient, delicious, and economical, new PET *Instant* may be helpful in dealing with the special dietary problems of many patients.

Instantized so it dissolves almost at the touch of water.

NEW PET INSTANT NONFAT DRY MILK

—PET MILK COMPANY • ST. LOUIS 1, MISSOURI—

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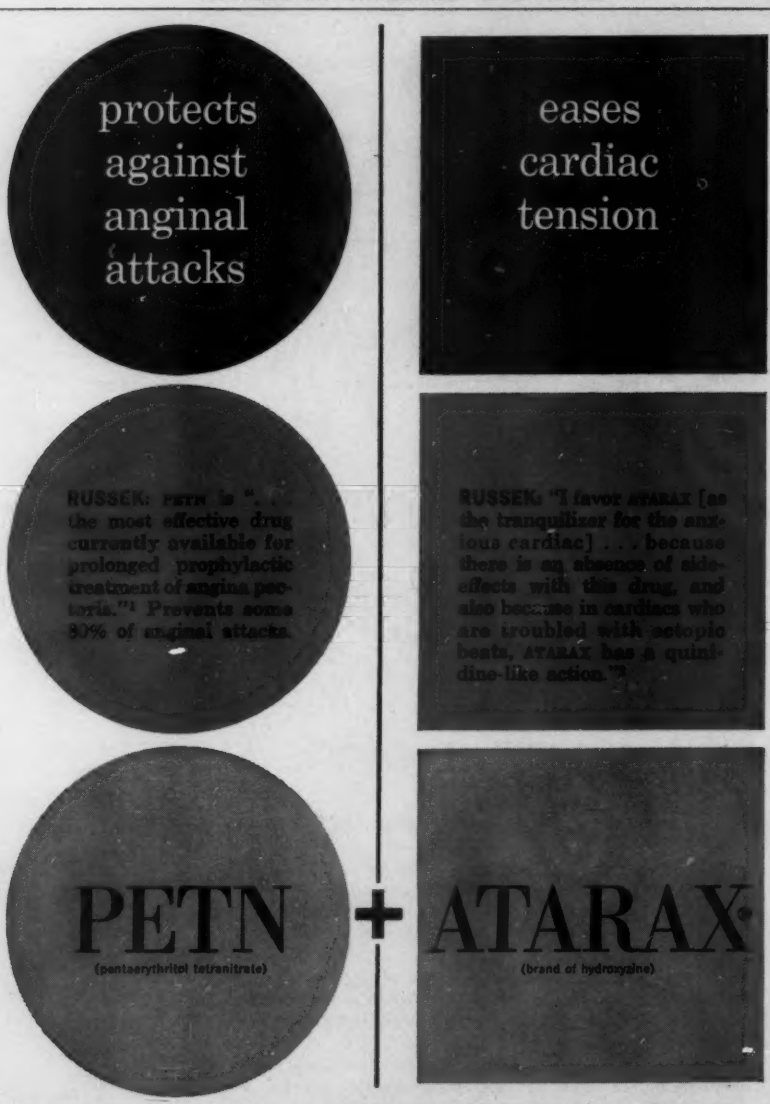
protects against anginal attacks
eases cardiac tension
RUSSEK: PETN is "... the most effective drug currently available for prolonged prophylactic treatment of angina pectoris."[1] Prevents some 80% of anginal attacks.
RUSSEK: "I favor ATARAX [as the tranquillizer for the anxious cardiac] . . . because there is an absence of side-effects with this drug, and also because in cardiacs who are troubled with ectopic beats, ATARAX has a quinidine-like action."[2]
PETN
(pentaerythritol tetranitrate)
+
ATARAX*
(brand of hydroxyzine)

CARTRAX*

(PETN + ATARAX)

Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX).

For convenience, write "CARTRAX 10" or "CARTRAX 20."

*TRADEMARK

Supplied: In bottles of 100.

References: 1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

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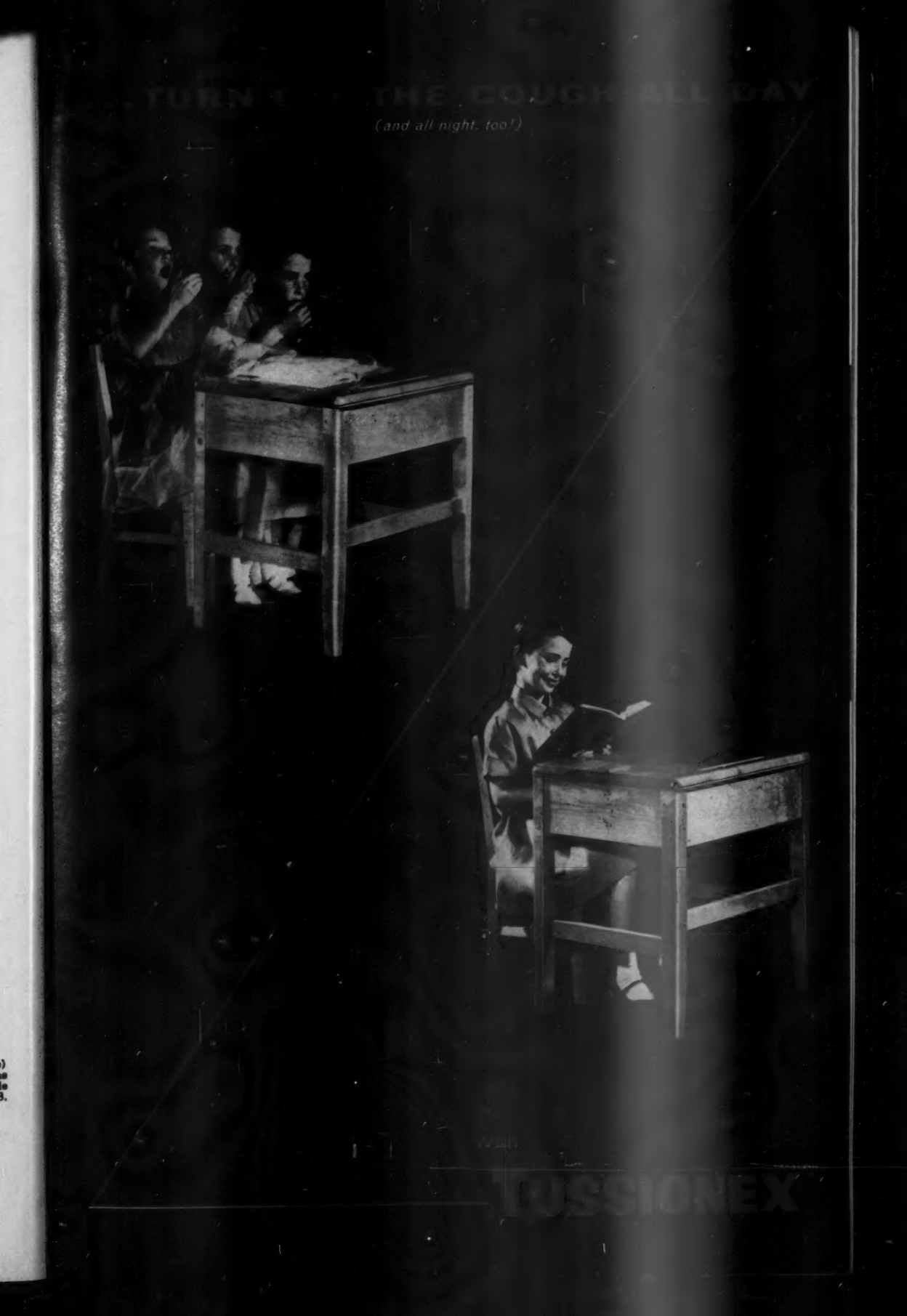
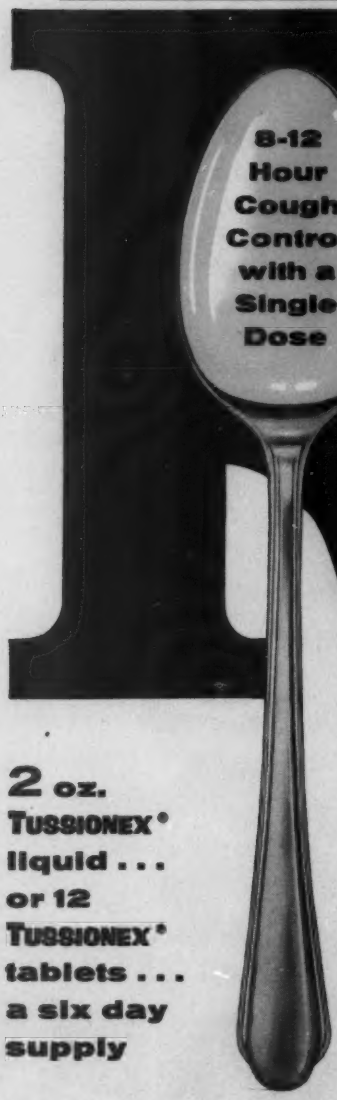
New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being


(and all night, too!)



Stop Useless Debilitating Cough of

Acute respiratory infections
Chronic sinusitis
Pharyngitis
Bronchitis
Postnasal drip
Bronchiectasis
Bronchogenic carcinoma
Cardiac decompensation
Pulmonary TB
Pulmonary TB with cold
Cigarette hack
Measles

2 oz. TUSSIONEX® liquid . . . or 12 TUSSIONEX® tablets . . . a six day supply

TUSSIONEX®

A 'Strasionic' Antitussive • Dihydrocodeinone Resin – Phenyltoloxamine Resin

Natural Protection of Cough Mechanism Not Impaired

Over 12,000 Clinical Observations Demonstrate Effectiveness

(1) Chan, Y. T. and Hays, E. E., The American Journal of the Medical Sciences, August 1957;

(2) Townsend, E. H., Jr., The New England Journal of Medicine, January 9, 1958;

(3) Case, Leo J. and Frederik, W. S., Annals of Internal Medicine, July 1958.

Adults:
1 tsp. or tablet q 12 h

Children:
Under 1 year.....¼ teaspoon q 12 h
1-5 years.....½ teaspoon q 12 h
Over 5 years..... 1 teaspoon q 12 h

Each teaspoonful (5c.c.) or tablet Tussionex provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes

Rx only. Class B taxable narcotic.

For Literature, Write

STRASENBURGH

Originators of 'Strasionic' (sustained ionic) Release

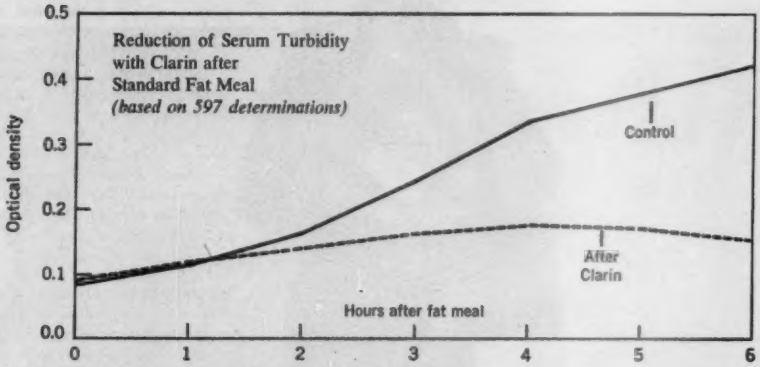
R. J. STRASENBURGH CO., ROCHESTER, N. Y., U.S.A.

in the management of atherosclerosis

Clarin*

(sublingual heparin potassium, Leeming)

clears lipemic serum



Each time your patients eat a substantial fat-containing meal, lipemia results. Small amounts of injected heparin will help control this increased fat content in the blood,[1,2] but widespread adoption of this method has been hampered by its inconvenience, pain, cost and the necessity for periodic checks on blood clotting time.

Now, long-term preventive heparin therapy is practical for the first time with the introduction of CLARIN—which is heparin in *sublingual* form. Each CLARIN tablet contains 1500 I.U. of heparin potassium—a sufficient amount to clear lipemic serum without affecting coagulation mechanisms.[3,4]

With one mint-flavored CLARIN tablet under the tongue after each meal, lipemia is regularly controlled, removing a constant source of danger to the atherosclerotic patient. He may eat safely, with less fear of dangerous results, without hard-to-follow diets.

The varied implications of CLARIN in beneficially affecting fat metabolism are obviously far-reaching. The relationship between heparin, lipid metabolism and atherosclerosis may well be analogous to that between insulin, carbohydrate metabolism and diabetes mellitus.[5]

Use CLARIN to protect your atherosclerotic patients—the postcoronaries and those with early signs of coronary artery disease.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Council on Drugs, J.A.M.A. *166*:52 (Jan. 4) 1958. 2. Hahn, P. F.: Science *98*:19 (July 2) 1943. 3. Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. 4. Rubio, F. A., Jr.: Personal communication. 5. Engelberg, H., *et al.*: Circulation *13*:489 (April) 1956.

*Trade Mark. Patent applied for.

Thos. Leeming & Co., Inc.

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Reported results with RONIACOL *in* intermittent claudication

FROM HALF A BLOCK TO TWO MILES. The patient, a 57-year-old white male with peripheral arteriosclerosis of about three years' duration, complained of pain in the right leg after walking half a block. After four weeks of treatment with Roniacol (75 mg per day), he was able to walk 20 blocks—and later two miles—without a sign of intermittent claudication. *Three years after discontinuing therapy*, "he still is able to walk unlimited distances and is without need of treatment."*

CONVERTED TO PURE VITAMIN IN THE BODY. Roniacol is not an adrenergic blocking agent; it is converted to the pure vitamin form (nicotinic acid) in the body and acts directly on the smooth muscle of the vascular wall.

EMINENTLY SAFE. There are *no known contraindications* to Roniacol. "Patients up to the ages of ninety have tolerated the drug in doses up to 600 mg with no adverse effects."*

*M. M. Fisher and H. S. Tobrach: New York State J. Med. 1945, 1953.

FROM HALF A BLOCK TO TWO MILES

Roniacol

RONIACOL®—brand of beta-pyridyl carbinol

Available in scored 50-mg tablets, bottles of 100, 500, and 1000. Roniacol Elixir, containing 50 mg of Roniacol per teaspoonful (5 cc), available in bottles of 16 ounces and one gallon.

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Division of Hoffmann-La Roche Inc
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ANNOUNCING

DIUPRES

DIURIL® WITH RESERPINE

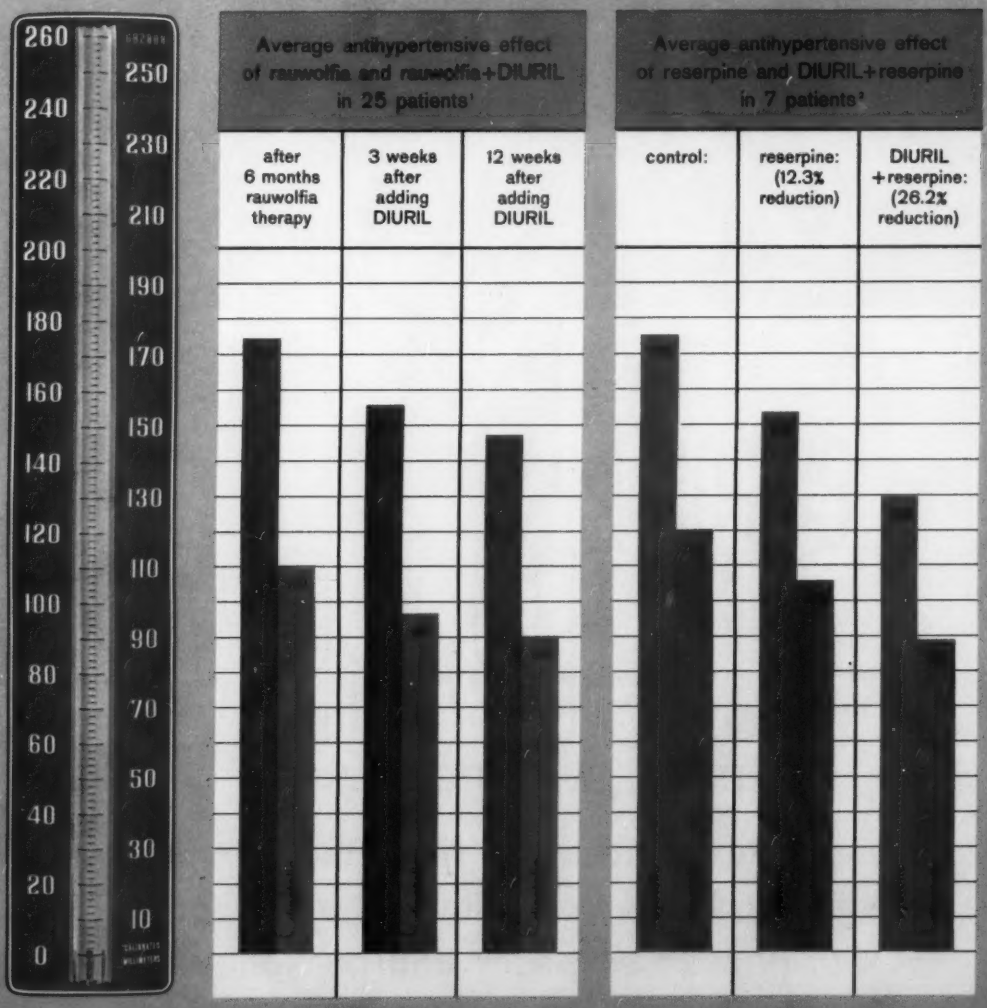
more hypertensives can be better controlled
with **DIUPRES** than with any other agent
... with greater simplicity and convenience

a logical alliance of two antihypertensives
you know and trust provides

increased effectiveness, decreased side effects

potentiated effect

DIUPRES produces an effect greater than either DIURIL or reserpine alone. It is effective in many patients who respond inadequately or not at all to either DIURIL or reserpine.



DIUPRES

DIURIL® WITH RESERPINE

effective therapy for most patients

DIUPRES by itself usually provides effective therapy for a majority of patients with mild or moderate hypertension, and even for many patients with severe hypertension. Many patients now treated with other agents which frequently cause distressing side effects can be adequately managed with well tolerated DIUPRES.

provides basic therapy

Should other drugs need to be added to DIUPRES, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.

rapid onset of effect

The antihypertensive action of DIUPRES is rapidly evident. (Considerable time may elapse before the antihypertensive effect of reserpine alone is observed.)

fewer and less severe side effects

DIUPRES may be expected to cause fewer and less severe side effects than are encountered with other antihypertensive therapy. (Since DIURIL and reserpine potentiate each other, the required dosage of each is usually less when given together as DIUPRES than when given alone. Such reduction in dosage makes side effects less likely to occur.)

often obviates weight gain

DIUPRES minimizes the problem of weight gain seen with reserpine (reserpine alone has been reported to produce weight gain in 50 per cent of patients).[1,4]

virtually eliminates fluid retention

DIUPRES is not likely to cause either clinical or subclinical retention of sodium and water. (Hypotensive drugs, particularly rauwolfia[5] and hydralazine,[6] may cause fluid retention. Even when such retention is subclinical, their antihypertensive effectiveness is diminished.[6])

diet more palatable

With DIUPRES, there is less need for rigid restriction of dietary salt, which patients find so burdensome.

> *"It may well be that the drug* [DIURIL] *produces the benefits of a markedly restricted low sodium diet but without its hardships."*[3]

subjective and objective improvement

DIUPRES allays anxiety and tension, thus reducing the emotional component of hypertension. Organic changes of hypertension may be arrested and reversed. Headache, dizziness, palpitations and tachycardia are usually promptly relieved by DIUPRES. When the *anginal syndrome* accompanies hypertension, the administration of DIUPRES may also cause diminution or even disappearance of this syndrome concurrent with control of the hypertension.

convenient, controlled dosage

Instead of two separate prescriptions, you write one prescription... the patient takes one tablet, rather than two different tablets... and the dosage schedule is easier for the patient to remember and follow.

> *"patients have fewer lapses and make fewer mistakes in dosage, the simpler the regimen can be made. Therefore I do not hesitate to use more than one medicament combined in one tablet, provided this gives approximately the correct dosage of each."*[6]

economical

DIUPRES will cost the patient less than if he were given two separate prescriptions for its components.

Indications:
DIUPRES is indicated in hypertension of all degrees of severity. It can be used in the following ways:

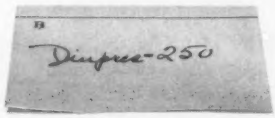
- as total therapy
- as primary therapy, adding other drugs if necessary
- as replacement or adjunctive therapy in patients now treated with other agents

Precautions:
The precautions normally observed with DIURIL or reserpine apply to DIUPRES. Additional information on DIUPRES is available to physicians on request.

Recommended dosage range:
DIUPRES-500—one tablet one to three times a day.
DIUPRES-250—one tablet one to four times a day.
If necessary, other agents may be added.
If the patient is receiving ganglion blocking agents or hydralazine, their dosage should be cut by 50 per cent when DIUPRES is added.

DIUPRES-500

500 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine.
Bottles of 100, 1000.



DIUPRES-250

250 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine.
Bottles of 100, 1000.

the first "wide range" antihypertensive

DIUPRES

DIURIL® WITH RESERPINE

1. Rochelle, J. B., III, Bullock, A. C., and Ford, R. V.: Potentiation of antihypertensive therapy by use of chlorothiazide, *J.A.M.A.* 168:410, Sept. 27, 1958. 2. Freis, E. D., Wanko, A., Wilson, I. M., and Parrish, A. E.: Treatment of essential hypertension with chlorothiazide (Diuril), *J.A.M.A.* 166:137, Jan. 11, 1958. 3. Freis, E. D.: Treatment of hypertension. (Presented at the Annual Meeting of Southern Medical Association, Nov. 13, 1957.) 4. Moyer, J. H., Dennis, E., and Ford, R.: Drug therapy (Rauwolfia) of hypertension, *A.M.A. Arch. Int. Med.* 96:530, Oct. 1955. 5. Perera, G. A.: Edema and congestive failure related to administration of rauwolfia serpentina, *J.A.M.A.* 159:439, Oct. 1, 1955. 6. Wilkins, R. W.: Precautions in use of antihypertensive drugs, including chlorothiazide, *J.A.M.A.* 167:801, June 14, 1958.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

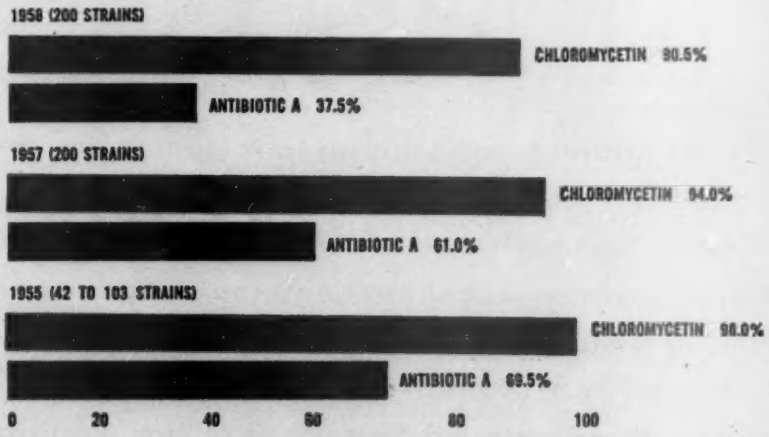
*DIUPRES and DIURIL (chlorothiazide) are trademarks of Merck & Co., Inc.

EFFECTIVE AGAINST MOST STRAINS OF STAPHYLOCOCCI

CHLOROMYCETIN®

COMBATS MOST CLINICALLY IMPORTANT PATHOGENS

IN VITRO SENSITIVITY OF PATHOGENIC STAPHYLOCOCCI TO CHLOROMYCETIN AND TO ANOTHER WIDELY USED BROAD-SPECTRUM ANTIBIOTIC FOR 1958, 1957, and 1955*



*Adapted from Holloway, W. J., & Scott, E. G.: *Delaware M. J.* 30:175, 1958. In this study CHLOROMYCETIN and Antibiotic A were used in identical strengths of 5 mcg.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

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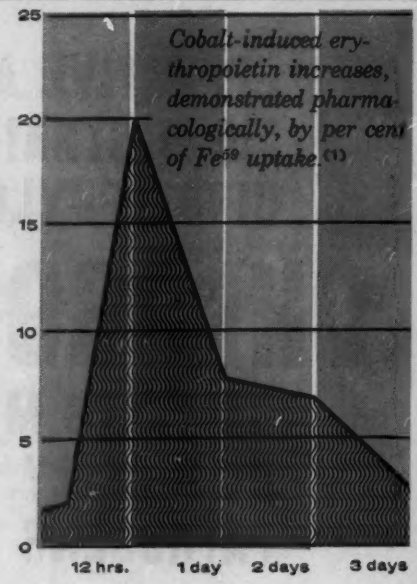

Cobalt-induced erythropoietin increases, demonstrated pharmacologically, by per cent of Fe^{59} uptake.(1)

Activates the physiologic mechanism in anemia therapy

RONCOVITE®-mf

Each tablet contains: Cobalt chloride (Cobalt as Co..3.7 mg.)..15 mg., Ferrous Sulfate, exsiccated..100 mg.

Only cobalt among therapeutic agents enhances production of erythropoietin to promote red cell formation.[1,2,3]

With Roncovite-MF, increased erythropoietin production permits excellent hematopoietic response with sharply reduced iron dosage.

Cobalt-iron (Roncovite therapy) has been demonstrated as superior to iron alone in the common hypochromic anemias such as menstrual anemia, anemia of pregnancy, nutritional anemia of infancy and refractory anemias of chronic infection.[4,5,6,7,8]

(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood 13:55 (Jan.) 1958. (2) Gurney, C. W.; Jacobson, L. O. and Goldwasser, E.: Ann. Int. Med. 49:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C.. and Bethell, F. H.: J. Lab. & Clin. Med. 52:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet 76:290 (Oct.) 1956. (5) Holly, R. G.: Obst. & Gynec. 9:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. 1:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinois M. J. 113:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas State J. Med. 51:686 (Oct.) 1955.

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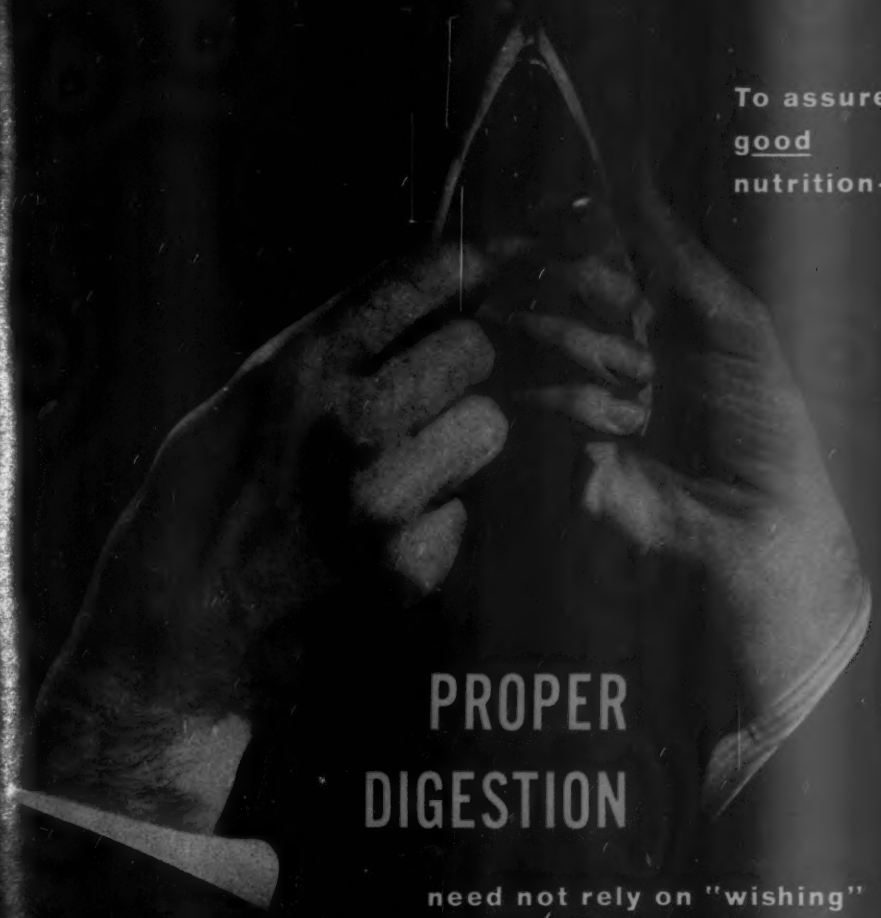


To assure good nutrition—

PROPER DIGESTION

need not rely on "wishing"

Each double layered Entozyme tablet contains:

Pepsin, N.F. 250 mg.
—released in the stomach from gastric soluble outer coating of tablet

Pancreatin, U.S.P. 300 mg.

Bile Salts 150 mg.
—released in the small intestine from enteric-coated inner core.

A. H. ROBINS CO., INC.
Richmond 20, Virginia
Ethical Pharmaceuticals of Merit since 1878

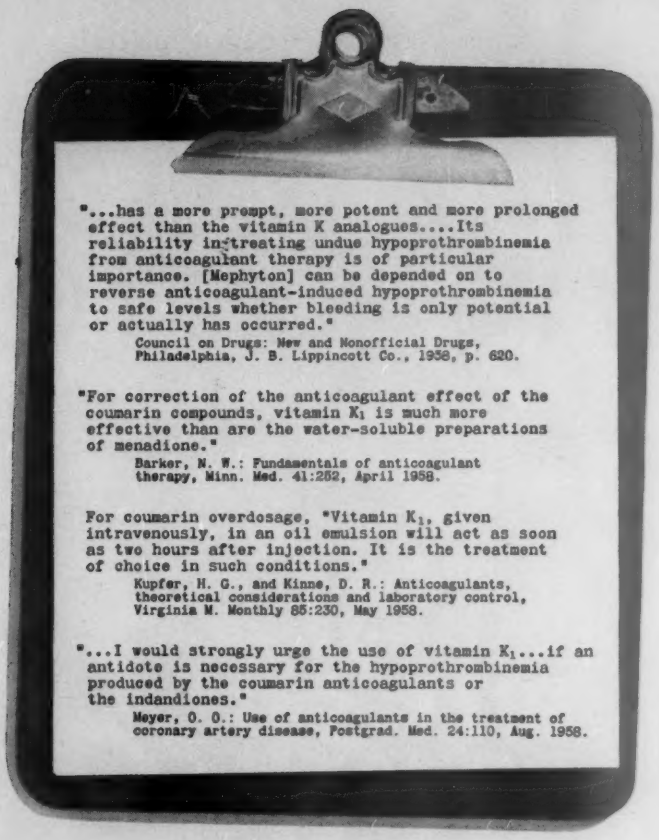
As a comprehensive supplement to deficient natural secretion of digestive enzymes, particularly in older patients, ENTOZYME effectively improves nutrition by bridging the gap between adequate ingestion and proper digestion. Among patients of all ages, it has proved helpful in chronic cholecystitis, post-cholecystectomy syndrome, subtotal gastrectomy, pancreatitis, dyspepsia, food intolerance, flatulence, nausea and chronic nutritional disturbances.

For comprehensive digestive enzyme replacement—

ENTOZYME

Robins

Consensus:
The preferred antidote for anticoagulant-induced hypoprothrombinemia is 'Mephyton' (vitamin K_1).



"...has a more prompt, more potent and more prolonged effect than the vitamin K analogues....Its reliability in treating undue hypoprothrombinemia from anticoagulant therapy is of particular importance. [Mephyton] can be depended on to reverse anticoagulant-induced hypoprothrombinemia to safe levels whether bleeding is only potential or actually has occurred."

Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1958, p. 620.

"For correction of the anticoagulant effect of the coumarin compounds, vitamin K_1 is much more effective than are the water-soluble preparations of menadione."

Barker, N. W.: Fundamentals of anticoagulant therapy, Minn. Med. 41:252, April 1958.

For coumarin overdosage, "Vitamin K_1, given intravenously, in an oil emulsion will act as soon as two hours after injection. It is the treatment of choice in such conditions."

Kupfer, H. G., and Kinne, D. R.: Anticoagulants, theoretical considerations and laboratory control, Virginia M. Monthly 85:230, May 1958.

"...I would strongly urge the use of vitamin K_1...if an antidote is necessary for the hypoprothrombinemia produced by the coumarin anticoagulants or the indandiones."

Meyer, O. O.: Use of anticoagulants in the treatment of coronary artery disease, Postgrad. Med. 24:110, Aug. 1958.

chemically identical with naturally-occurring vitamin K_1

Mephyton®

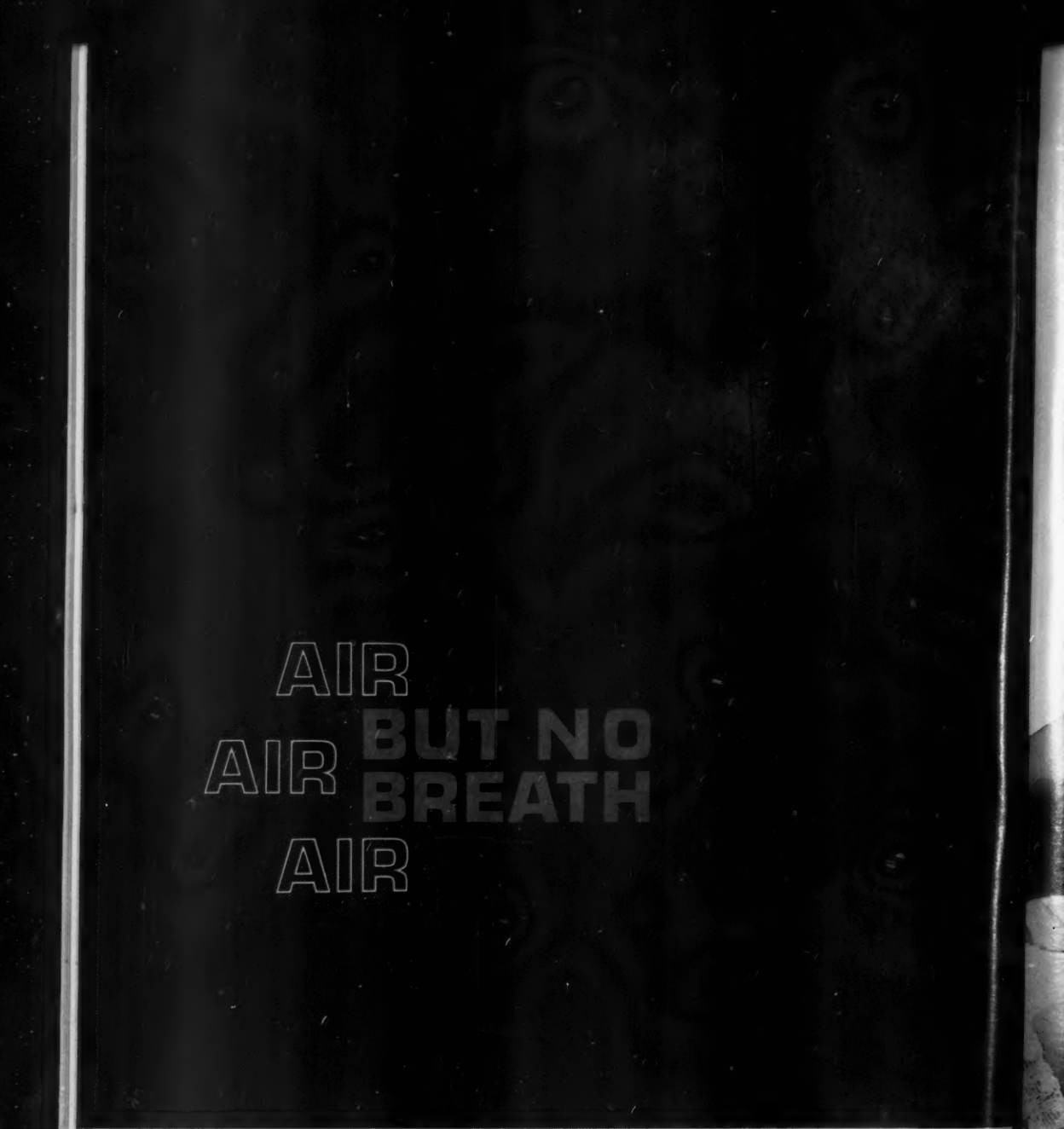
Vitamin K_1

Dosage: Orally, to modify anticoagulant effects: 5 to 10 mg. initially; 15 to 25 mg. for more vigorous action. Intravenously, for anticoagulant-induced bleeding emergencies, 10 to 50 mg.; may be repeated as indicated by prothrombin time response. (Some clinicians advise their patients to keep a supply of tablets on hand at all times; if gross bleeding occurs, the patients are instructed to take 10 mg. and phone the doctor.)

Supplied: Tablets, 5 mg.; bottles of 100. Emulsion, each 1-cc. ampul contains 50 mg.; boxes of 6 ampuls.

MEPHYTON is a trademark of Merck & Co., Inc.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.



IN EMPHYSEMA, CHRONIC BRONCHITIS and other pulmonary disorders, Choledyl effectively relieves bronchospasm and increases vital capacity. After two weeks on Choledyl, patients usually display a marked reduction in wheezing and coughing . . . breathing becomes easier. Well-tolerated, highly soluble Choledyl provides long-term protection in patients of all ages.

CHOLEDYL®
(brand of oxtriphylline)

betters breathing...forestalls the crisis

WARNER CHILCOTT
MORRIS PLAINS, N. J.

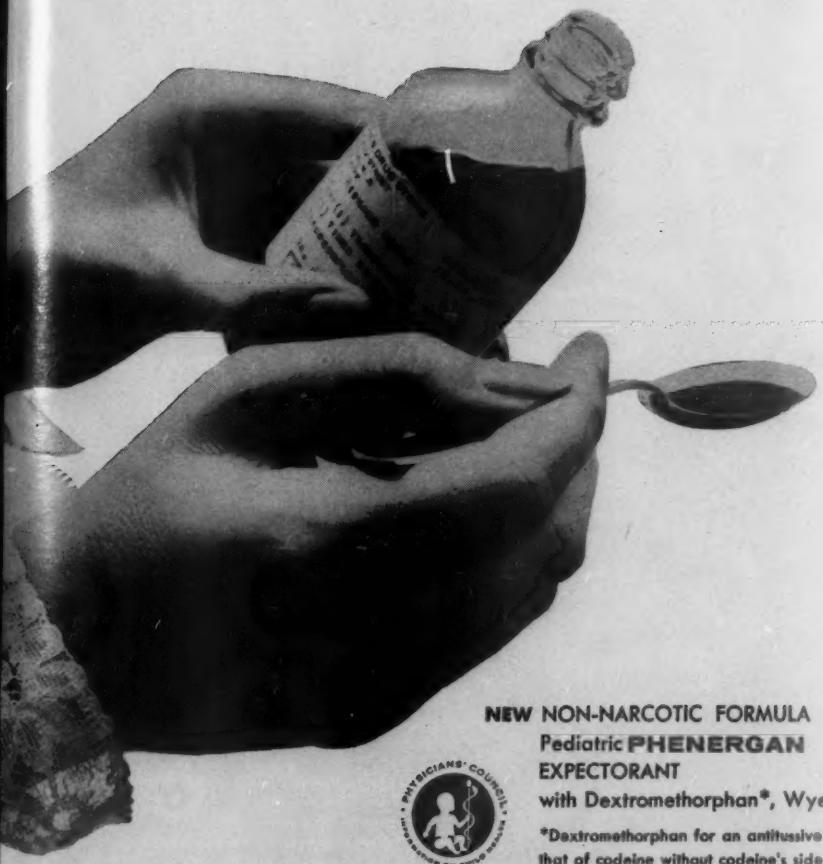
quiets the cough

and calms the patient . . .

Expectorant action
Antihistaminic action
Sedative action
Topical anesthetic action

PHENERGAN®
EXPECTORANT
Promethazine Expectorant, Wyeth
with Codeine Plain (without Codeine)

Wyeth®
Philadelphia 1, Pa.



NEW NON-NARCOTIC FORMULA
Pediatric PHENERGAN
EXPECTORANT
with Dextromethorphan*, Wyeth

*Dextromethorphan for an antitussive action equivalent to that of codeine without codeine's side-effects

CONFORMS TO CODE FOR ADVERTISING

In Chicago Visit Our Exhibit, Booths 142, 143, 144 and 145

Author of the classic "Bodily Changes in Pain, Hunger, Fear and Rage," pathfinder in experimental physiology,

(1871-1945) demonstrated conclusively the effect of emotions on the G.I. tract.

in G.I. symptoms of anxiety states

®Miltown + *anticholinergic*

provides relief of pain, spasm, anxiety and tension without belladonna or barbiturates. Side effects are minimal.

Each scored tablet contains:
meprobamate 400 mg., tridihexethyl chloride 25 mg.
(formerly supplied as the iodide)

1 tablet t.i.d. with meals and 2 tablets at bedtime.

duodenal and gastric ulcer • colitis
spastic and irritable colon • gastric hypermotility • gastritis
esophageal spasm • intestinal colic • functional
diarrhea • G.I. symptoms of anxiety states.

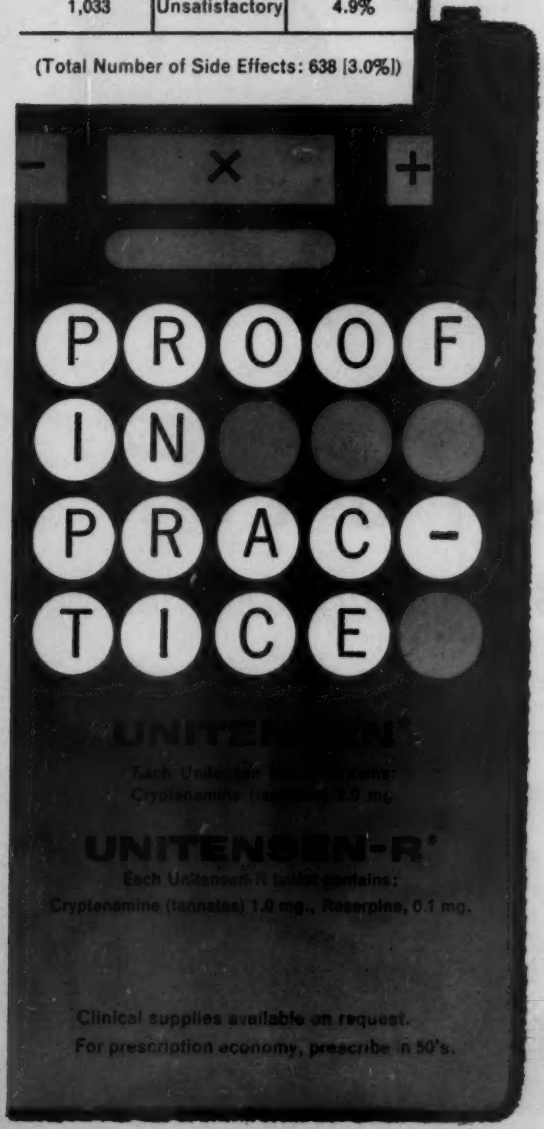
Literature and samples on request.

WALLACE LABORATORIES
New Brunswick, N. J.

SUMMARY OF REPORTS

No. of Patients	Results	Percent
6,553	Excellent	31.0%
10,843	Good	51.3%
2,703	Fair	12.8%
1,033	Unsatisfactory	4.9%

(Total Number of Side Effects: 638 [3.0%])



A NEW DIMENSION IN RESEARCH

This data deals with the results obtained by 1,988 physicians, treating 21,128 hypertensive patients with Unitensen. The "Proof In Practice" study validates, *in day-to-day private practice*, the findings of clinical trials conducted in hospitals and institutions. It proves that Unitensen affords safe, dependable office management for the majority of hypertensive patients. Unitensen lowers blood pressure . . . improves cerebral and renal blood flow... exerts no adverse effects on circulation . . . and, is virtually free of side effects.

Neisler

Irwin, Neisler & Co.
Decatur, Illinois

In Chicago Visit Our Exhibit, Booth 14

in vaginitis

IMPROVED

TRICOFURON®

destroys all 3 *principal pathogens*

Whether vaginitis is caused by Trichomonas, Monilia or Hemophilus vaginalis—alone or combined—TRICOFURON IMPROVED swiftly relieves symptoms and malodor, and achieves a truly high percentage of cultural cures, frequently in 1 menstrual cycle. TRICOFURON IMPROVED provides: a *new* specific moniliacide MICOFUR® brand of nifuroxime, the *established* specific trichomonacide FUROXONE® brand of furazolidone and the *combined* actions of both against Hemophilus vaginalis.

1. *Office* insufflation once weekly of the Powder (MICOFUR [*anti*-5-nitro-2-furaldoxime] 0.5% and FUROXONE 0.1% in an acidic water-soluble powder base). **2.** Continued *home* use twice daily, with the Suppositories (MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base).

℞ NEW BOX OF 24 SUPPOSITORIES WITH APPLICATOR FOR MORE PRACTICAL AND ECONOMICAL THERAPY.

NITROFURANS—a *new* class of antimicrobials—neither antibiotics nor sulfonamides.

EATON LABORATORIES, NORWICH, NEW YORK

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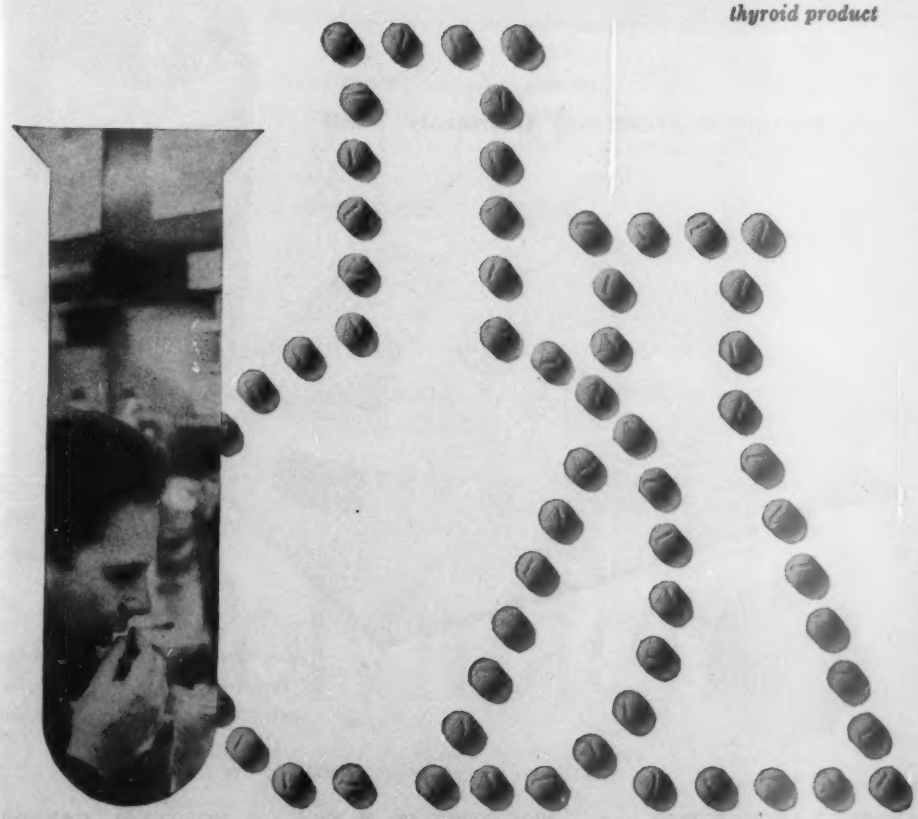
THE PIONEER IN THYROID STANDARDIZATION

Armour thyroid tablets assure: Consistent response—unsurpassed quality—highest manufacturing standards—full potency up to 17 years of storage—dependable therapy in: frank thyroid deficiencies and when hypothyroidism is associated with chronic recurrent colds, functional menstrual disorders, sterility, habitual abortion, obesity, hypometabolism. Thyroid is recommended in long-term therapy with ACTH or corticosteroids. Supplied in ¼, ½, 1, 2 and 5 grain strengths.

specify **ARMOUR THYROID**

the most widely prescribed thyroid product



ARMOUR PHARMACEUTICAL COMPANY • KANKAKEE, ILLINOIS / *a leader in biochemical research*

PMB-200

"Premarin" with Meprobamate

Each tablet contains 0.4 mg. "Premarin," 200 mg. meprobamate.

PMB ("Premarin" with Meprobamate) is an ideal preparation when the patient needs extra relief from anxiety and tension during the menopause. Once these symptoms are under control, therapy may be continued with "Premarin" alone.

Simple to prescribe as merely PMB

Supply: No. 880, PMB-200, bottles of 60 and 500.

Also available No. 881, PMB-400 ("Premarin" 0.4 mg. with meprobamate 400 mg.), bottles of 60 and 500.

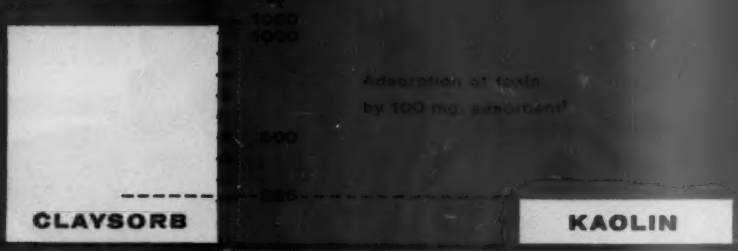
Ayerst

AYERST LABORATORIES • NEW YORK 16, N. Y. • MONTREAL, CANADA

5827 "Premarin"® conjugated estrogens (equine) Meprobamate, licensed under U.S. Pat. No. 2,724,720

in diarrhea . . .

adsorptive power



CLAYSORB is 5 times as adsorptive as kaolin

When you prescribe POLYMAGMA or POLYMAGMA Plain to control diarrhea, you are prescribing adsorptive superiority. Both preparations contain Claysorb—a new intestinal adsorbent whose superiority over kaolin has been demonstrated in exhaustive studies.[1,2,3]

For *bacterial* diarrhea, POLYMAGMA is bactericidal to many intestinal pathogens. It is soothing and protective to the irritated mucosa. It aids in the restoration of normal intestinal function. Highly effective, highly palatable.

For *nonbacterial* diarrhea, POLYMAGMA Plain—same formula but without antibiotics.

1. Barr, M., and Arnista, E.S.: J. Am. Pharm. A. (Scient. Ed.) *46*:493 (Aug.) 1957. 2. Barr, M., and Arnista, E.S.: *Ibid.* *46*:486 (Aug.) 1957. 3. Barr, M.: *Ibid.* *46*:490 (Aug.) 1957.

Polymagma®

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel

Wyeth®
Philadelphia 1, Pa.

*Trademark

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health.

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in peptic ulcer

KOLANTYL with 4 needed healing actions

1. vital antispasmodic action—BENTYL—Merrell's fast, safe antispasmodic . . . relieves spasm-pain promptly, without atropine-like side effects. 2. balanced acid-neutralizing action—magnesium oxide and aluminum hydroxide—prompt, long-lasting relief . . . no laxation, no constipation. 3. demulcent action—Methylcellulose—soothing protective coating covers ulcerated area, promotes healing. 4. antienzyme-antipepsin action—Sodium Lauryl Sulfate—effectively curbs necrotic effects of pepsin and lysozyme . . . prevents further erosion. Dosage—Gel: 2 to 4 teaspoonfuls every 3 hours, or as needed. Tablets: 2 tablets (chewed for more rapid action) every 3 hours, or as needed. NON-CONSTIPATING . . . NON-LAXATING

TRADEMARKS: "BENTYL," "KOLANTYL"

Merrell

THE WM. S. MERRELL COMPANY
New York • CINCINNATI • St. Thomas, Ontario
Another Exclusive Product of Original Merrell Research

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KENACORT

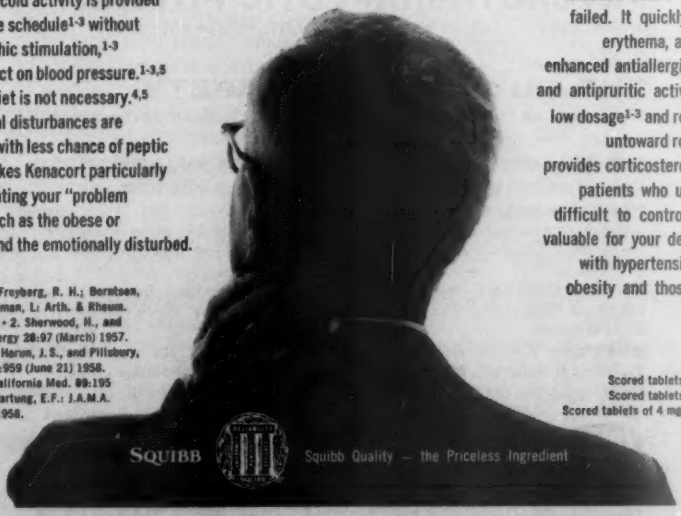
SQUIBB TRIAMCINOLONE

for all your patients starting on corticoids

Kenacort safely starts your patients off right — with all the benefits of systemic corticosteroid therapy and few side effects to worry about. Increased corticoid activity is provided on a low dosage schedule[1-3] without edema,[1-4] psychic stimulation,[1-3] or adverse effect on blood pressure.[1-3,5] A low sodium diet is not necessary.[4,5] Gastrointestinal disturbances are negligible[2,4,5] with less chance of peptic ulcer.[4] This makes Kenacort particularly valuable in treating your "problem patients" — such as the obese or hypertensive and the emotionally disturbed.

for all your patients with dermatoses requiring corticoids

Kenacort, particularly in treating inflammatory skin conditions, has proved effective where other steroids have failed. It quickly alleviates itching, erythema, and irritation with its enhanced antiallergic, anti-inflammatory and antipruritic activity. Because of its low dosage[1-3] and relative freedom from untoward reactions,[1-5] Kenacort provides corticosteroid benefits to many patients who until now have been difficult to control. It is particularly valuable for your dermatologic patients with hypertension, cardiac disease, obesity and those prone to psychic disturbances.



REFERENCES: • 1. Freyberg, R. H.; Bornstein, C. A., Jr., and Hellman, L: Arth. & Rheum. 1:215 (June) 1958. • 2. Sherwood, N., and Cooke, R. A.: J. Allergy 28:97 (March) 1957. • 3. Shelley, W. B.; Haroun, J. S., and Pillsbury, D. M.: J.A.M.A. 167:959 (June 21) 1958. • 4. Dubois, E.L.: California Med. 89:195 (Sept.) 1958. • 5. Hartung, E.F.: J.A.M.A. 167:973 (June 21) 1958.

SUPPLIED:
Scored tablets of 1 mg. — Bottles of 50
Scored tablets of 2 mg. — Bottles of 50
Scored tablets of 4 mg. — Bottles of 30 and 100

SQUIBB Squibb Quality — the Priceless Ingredient

"KENACORT" ® IS A SQUIBB TRADEMARK

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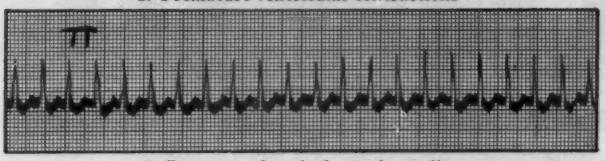
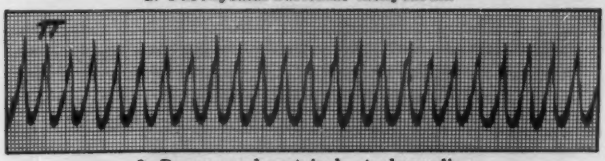
restore normal sinus rhythm

1. Premature ventricular contractions



2. Paroxysmal auricular tachycardia



3. Paroxysmal ventricular tachycardia

in arrhythmias

VISTARIL*

HYDROXYZINE PAMOATE

More than a tranquilizer

SPECIFIC ANTIARRHYTHMIC EFFECT

Vistaril is effective in ventricular extrasystoles and paroxysmal tachycardias (both auricular and ventricular).

plus

PSYCHOTHERAPEUTIC POTENCY

proven calming action indicated for arrhythmia patients.

and

THE OUTSTANDING SAFETY

of Vistaril as compared to other antiarrhythmic drugs in general use has been noted by investigators.

THE FOLLOWING DOSAGE REGIMEN IS RECOMMENDED (individualized by the physician for maximum effectiveness):

PARENTERAL DOSAGE: 50-100 mg. (2-4 cc.) I.M. stat., and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d. In acute emergency, 50-75 mg. (2-3 cc.) I.V. stat.; maintain with 25-50 mg. (1-2 cc.) I.V. q. 4-6 h., p.r.n.

ORAL DOSAGE: Initially, 100 mg. daily in divided doses until arrhythmia disappears. For maintenance or prophylaxis, 50-75 mg. daily in divided doses.

SUPPLY: Vistaril Capsules, 25 mg., 50 mg. and 100 mg. Vistaril Parenteral Solution, 10 cc. vials and 2 cc. Steraject® Cartridges. Each cc. contains 25 mg. (as the hydrochloride).

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

References: 1. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 2. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

*Trademark

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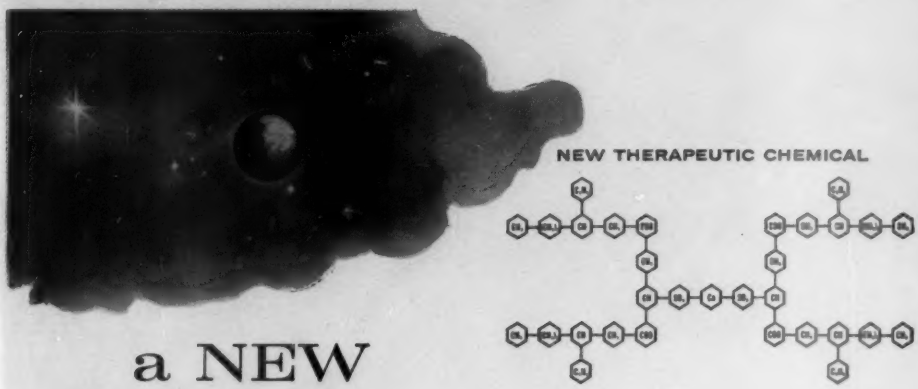

a NEW
DIMENSION
IN THE
TREATMENT OF CONSTIPATION

DOXIDAN

The Surfactant Laxative

"Ideal" laxative therapy has now been made possible by the application of a new principle based on the double surfactancy of the new therapeutic chemical, calcium bis-(dioctyl sulfosuccinate).

Doxidan provides positive, reliable laxative action with:

- Greatly reduced laxative dosage and optimal surfactancy.
- The least possible disturbance of normal body physiology.
- Freedom from the discomfort of bowel distention.
- Freedom from "oily leakage" and interference with vitamin absorption.
- Freedom from pain and "cramping."
- Greatly reduced risk of laxative habituation.

No longer is a "cathartic flush" needed to expel a hardened resistant fecal mass. Instead, once calcium bis-(dioctyl sulfosuccinate) has rendered the mass malleable and mobile, a gentle peristaltic stimulant is all that is needed to correct bowel dysfunction.

Doxidan is a true synergistic combination of calcium bis-(dioctyl sulfosuccinate), the new surfactant fecal softener, and Danthron, a mild peristaltic stimulant which acts solely in the lower bowel.

This new dimension in treatment (Doxidan therapy) results in soft, "normal" stools gently stimulated to evacuation.

Each maroon soft gelatin capsule contains 50 mg. Danthron (1,8-dihydroxyanthraquinone) and 60 mg. calcium bis-(dioctyl sulfosuccinate).

dosage: For adults and children over 12, one or two capsules. For children, age 6 to 12, one capsule. Give at bedtime for 2 or 3 days or until bowel movements are normal.

supplied: Bottles of 30 and 100 soft gelatin capsules.

LLOYD BROTHERS, INC. CINCINNATI 3, OHIO

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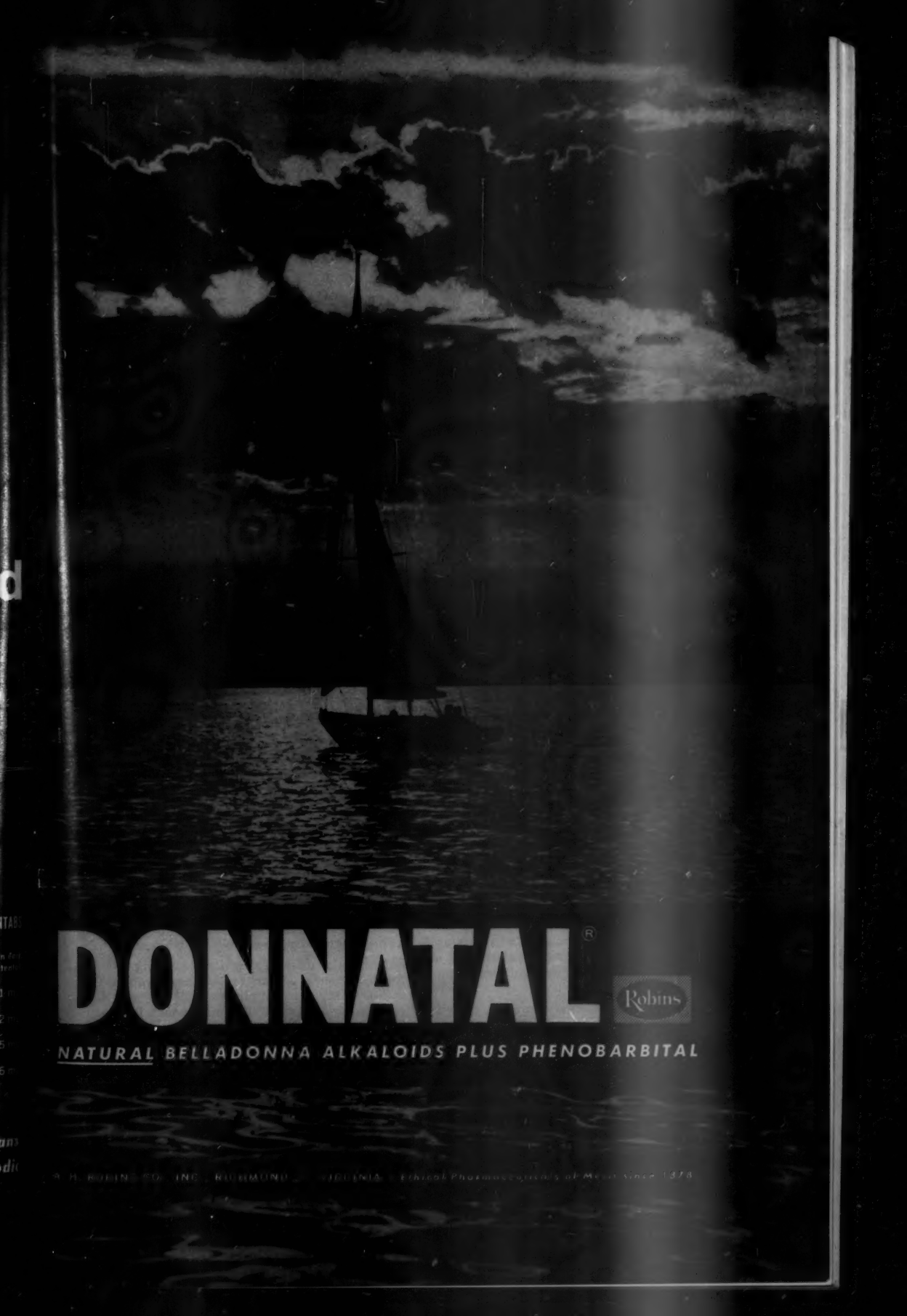
Like oil on troubled waters

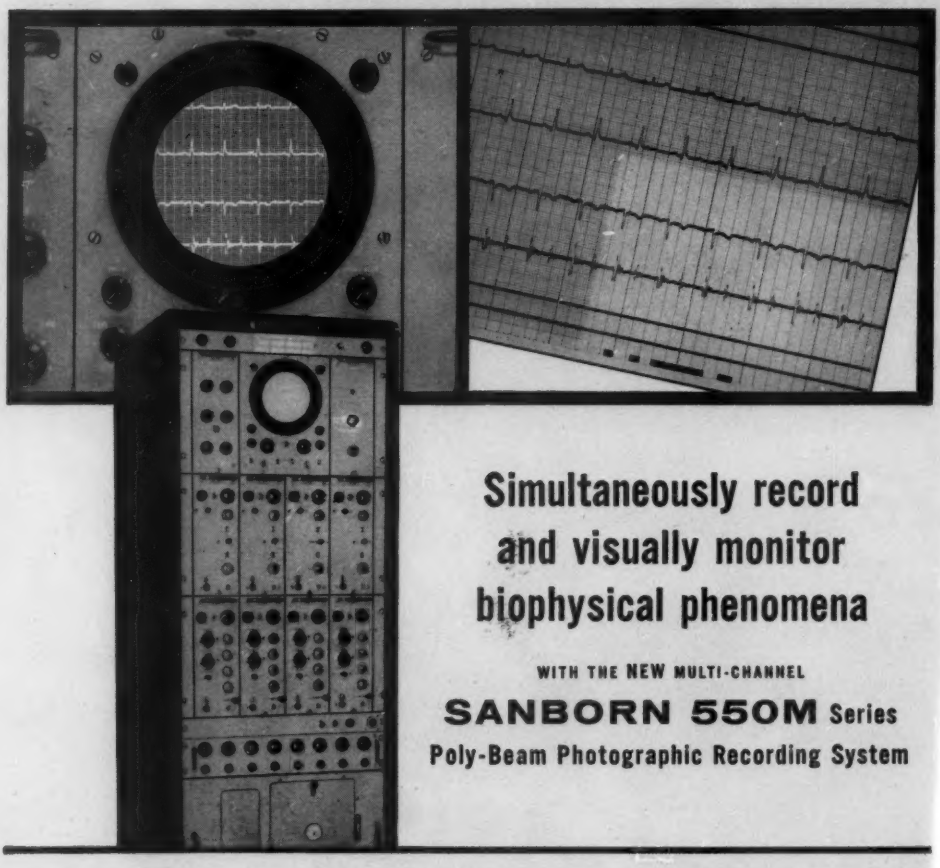
When smooth muscle spasm gets rough on your patients...

TABLETS • CAPSULES • ELIXIR • EXTENTABS

	In each Tablet, Capsule or fl.dr. (5 cc.) of Elixir	In Extentabs
Hyoscyamine sulfate	0.1037 mg.	0.1 mg.
Atropine sulfate	0.0194 mg.	0.0582 mg.
Hyoscine hydrobromide	0.0065 mg.	0.0195 mg.
Phenobarbital	(¼ gr.) 16.2 mg.	(¾ gr.) 48.6 mg.

Prescribed by more physicians than any other antispasmodic


DONNATAL®
Robins
NATURAL BELLADONNA ALKALOIDS PLUS PHENOBARBITAL



Simultaneously record and visually monitor biophysical phenomena

WITH THE NEW MULTI-CHANNEL

SANBORN 550M Series

Poly-Beam Photographic Recording System

SPEED and SENSITIVITY of the 550M System permit diagnostically accurate recording of fast changing phenomena such as heart sounds and small-animal ECG's and of low-level signals such as small-muscle myograms, EEG and fetal ECG.

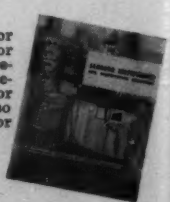
VERSATILITY and FLEXIBILITY of the 550M design offer many advantages. The system can be purchased with only 4 or 6 channels and minus the monitoring unit. Additional *interchangeable* plug-in preamplifiers (up to a total of 8), plug-in mirror galvanometer inserts and the visual monitoring unit – consisting of an electronic switch, vector timer and oscilloscope – can be added later.

ADDITIONAL FEATURES Include: entire 6 inch chart width available to all beams...ability of beams to be *superimposed* and to *cross* each other...photographically registered *timing* and *amplitude lines* . . . trace interrupter for *beam identification* . . . provision for *elimination of amplitude lines* from part or all of the record . . . choice of 8 chart speeds from 1.25 to 200 mm/sec . . . display on the monitoring unit of up to four waveforms at once, or vector loops, as either a substitute for or a supplement to the recorder . . . exposed film container can be removed at any time under normal light . . . event marker included . . . provision made for remote control . . . viewing window permits observing and positioning of galvanometer beams.

The new 550M Poly-Beam is a completely self-contained recording – monitoring system built into a single, mobile cabinet only 22" wide and 6' high.

Sanborn also offers a new *direct-writing* recorder, the 350M Series – in a 6- or 8-channel system. Plug-in "350" style preamplifiers can be used interchangeably with the 550M Series which is identical in cabinet size and style.

Write for the new 8-page 550M catalog, or the complete catalog describing the major Sanborn instruments for measuring, recording or monitoring biophysical phenomena. The Sanborn Branch Office or Service Agency nearest you can also supply complete information on any or all Sanborn equipment.



SANBORN COMPANY

MEDICAL DIVISION

175 Wyman Street, Waltham 54, Massachusetts

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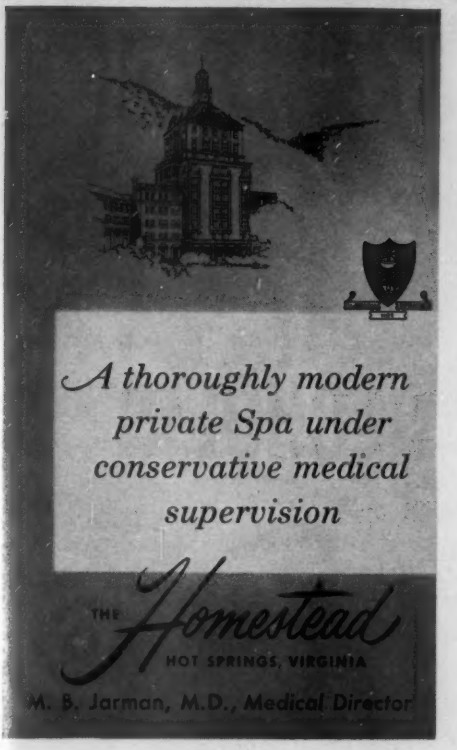

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HOW PREVALENT ARE MULTIPLE GALLBLADDER ANOMALIES?

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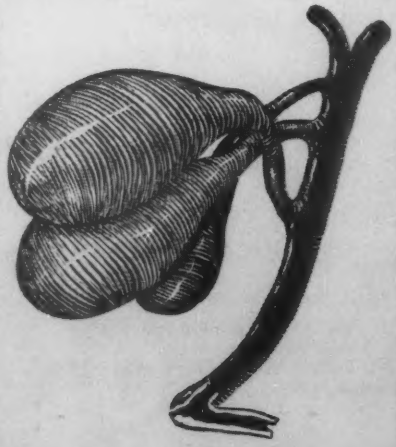
Source: Skilboe, B.: Am. J. Clin. Path. *30*:252, 1958.



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(1) Beckman, H.: Drugs: Their Nature, Action and Use, Philadelphia, W. B. Saunders Company, 1958, p. 425.
(2) Biliary Tract Diseases, M. Times *85*:1081, 1957.

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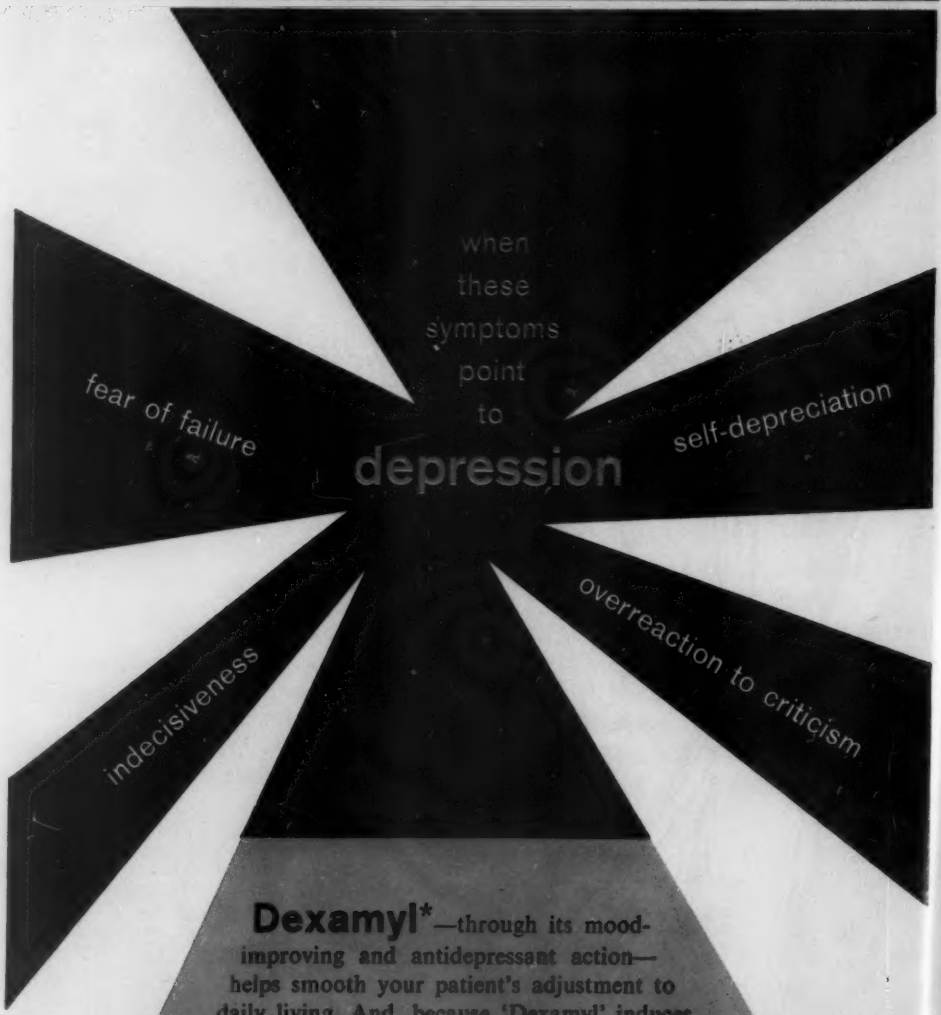

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	April					May				June			
	2–4	6–10	13–17	20–24	27–May 1	4–8	11–15	18–22	25–29	1–5	8–12	15–19	22–26
Course No. 1, THE PRACTICE OF GLOBAL MEDICINE IN THE UNITED STATES: Cornell University Medical College, New York, N. Y.; Benjamin H. Kean, M.D., (Associate), Director.	*			A.C.P. Annual Session, Chicago, Illinois							A.M.A. Annual Meeting, Atlantic City		
Course No. 2, PRACTICAL REHABILITATION PROCEDURES FOR THE INTERNIST: University of New York, Institute of Physical Medicine and Rehabilitation, Bellevue Medical Center, New York, N. Y.; Howard A. Rusk, M.D., F.A.C.P., Director; Edward W. Lowman, M.D., F.A.C.P., and Donald A. Covalt, M.D., Co-directors.			13, 14, 15										
Course No. 3, CARDIAC ARRHYTHMIAS: Philadelphia General Hospital, Philadelphia, Pa.; Samuel Bellet, M.D., F.A.C.P., Director.								22, 23, 24					
Course No. 4, PSYCHIATRY FOR THE INTERNIST: Psychiatric Institute, University of Maryland Hospital, Baltimore, Md.; Leo H. Bartemeier, M.D., F.A.C.P., and Ephraim T. Lisansky, M.D., F.A.C.P., Co-directors.										*			
Course No. 5, SPECIAL TOPICS IN INTERNAL MEDICINE: University of Colorado Medical Center, Denver, Colo.; Gordon Meiklejohn, M.D., F.A.C.P., and C. Wesley Eisele, M.D., F.A.C.P., Co-directors.												*	
Course No. 6, INTERNAL MEDICINE; SELECTED TOPICS: Cincinnati General Hospital, University of Cincinnati College of Medicine, Cincinnati, Ohio; Richard W. Vilter, M.D., F.A.C.P., Director, and John R. Braunstein, M.D., F.A.C.P., Associate Director.													*

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1. Kirsner, J.B., et al.: M. Clin. North America *41*:499 (March) 1957.

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1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958.
2. Current personal communications; in the files of Wallace Laboratories.

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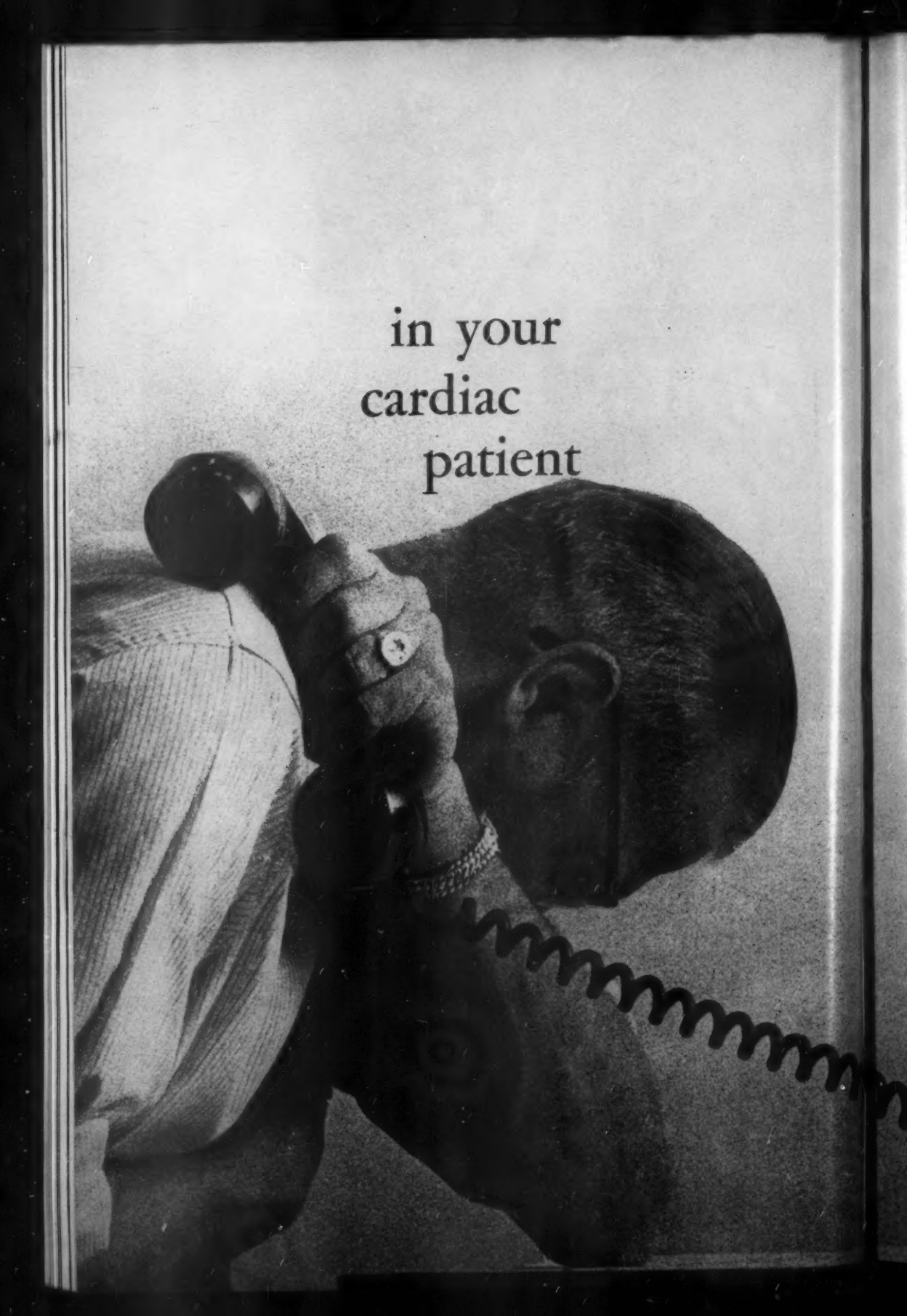
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ANNALS OF
INTERNAL MEDICINE

VOLUME 50 FEBRUARY, 1959 NUMBER 2

BLOOD ABSORPTIVE PATTERNS OF ISOTOPICALLY-LABELED FAT AND FATTY ACID*

By DONALD BERKOWITZ, M.D., DAVID SKLAROFF, M.D., ASHER WOLDOW, M.D., A. GERSON JACOBS, M.D., and WILLIAM LIKOFF, M.D., F.A.C.P.,
Philadelphia, Pennsylvania

CLINICAL conditions associated with abnormal lipid metabolism fall into two general categories: (1) those arising from decreased intestinal absorption, and (2) those produced by a derangement in utilization, transport or storage. Various primary and secondary malabsorption syndromes, including idiopathic sprue and pancreatogenous steatorrhea, are classified in the first group, while the essential lipoidoses, atherosclerosis and possibly obesity are believed to belong in the second.

Several methods are available which aid in assaying abnormal fat metabolism. These include biochemical measurements of specific blood constituents, such as cholesterol, lipids or lipoprotein fractions, intubation studies which quantitate pancreatic secretions, and stool analyses to gauge fat excretion. Each of these technics involves many difficulties on the part of the patient, the nursing staff and the laboratory. Moreover, each is concerned with only one facet of the entire problem.

Through the use of radioactive fat a new tool is now available. The material may be obtained in the form of the triglyceride, triolein, or as the free fatty acid, oleic acid. Activity is imparted to these compounds by the addition of I^{131} to the double bond in the oleic acid molecule. Chemical and electrophoretic evidence has shown that when these tagged lipids are ingested

* Presented at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, May 2, 1958.

From the Departments of Medicine and Radiology, Albert Einstein Medical Center, Northern Division, the Hahnemann Medical College, and the Sidney Hillman Medical Center at the Male Apparel Industry, Philadelphia, Pennsylvania.

Supported in part by a grant from the Southeastern Heart Association of Pennsylvania.

Requests for reprints should be addressed to Donald Berkowitz, M.D., 101 South Twentieth Street, Philadelphia 3, Pennsylvania.

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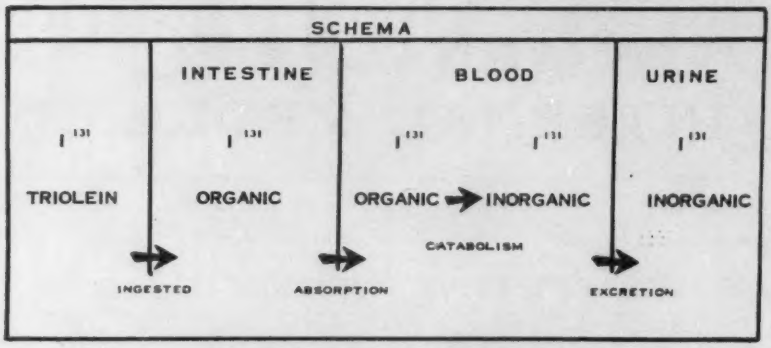

FIG. 1. Metabolism of orally ingested radioactive fat.

they undergo changes similar to nonradioactive lipids.[1] Their use in the study of fat metabolism therefore appears to be sound.

The technic utilizing radioactive fat has been described previously.[2] It consists essentially of the administration of a fat meal containing 25 microcuries of I^{131}-triolein or oleic acid in a total volume of 1 ml./Kg. of body weight of peanut oil. Thereafter venous blood samples are withdrawn periodically until a maximal radioactivity level has been reached, and then again after 24 hours. The radioactivity in each sample, as well as the 24-hour urine and stool collections, is determined and expressed as a percentage of the initially ingested fat.

The radioactive iodine circulates in the blood in two forms: organic, in which it is attached to the lipo-protein molecule, and in an inorganic fraction, which is derived after the fatty acid bond has been split during utiliza-

TABLE 1

Uses of Radioactive Fat Tolerance Tests

1. Diagnostic Evaluation
   - Steatorrhea
   - Pancreatic disease
   - Jaundice
2. Evaluation of Degree of Fat Malabsorption
   - Regional ileitis
   - Whipple's disease
   - Lymphosarcoma of intestine
   - Gastrocolic fistula
   - Postgastrectomy state
   - Liver disease
   - Congestive heart failure
   - Sprue
3. Metabolic Studies
   - Coronary atherosclerosis
   - Hypercholesterolemia
   - Obesity
   - Mixed meals

tion (figure 1). The quantity of the latter is determined by the rate of fat catabolism and renal excretion. These two portions may be separated in the blood samples by adding trichloracetic acid. Normally the organic part does not exceed 50% of the total.

The essential features of the blood radioactivity curves include (1) the time of maximal blood radioactivity, (2) the magnitude of this maximal value, (3) the 24-hour activity level, and (4) the organic fraction/whole

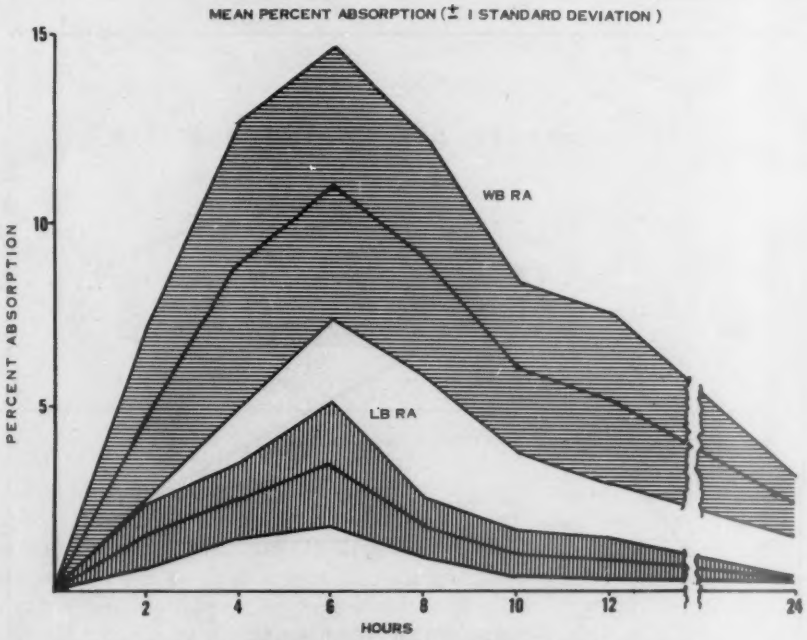

FIG. 2. Radioactive fat absorption in normal subjects (WB = whole blood, LB = lipid blood, RA = radioactivity).

blood radioactivity ratio. Although these values are only a partial reflection of the complete metabolic cycle which ensues after a labeled fat test meal, they appear to be the most informative.

Our experience to date with this technic includes over 500 studies. This report attempts to define those conditions in which a labeled fat tolerance test is of value (table 1).

1. *Normal Values* (figure 2): After ingestion of a triolein test meal, the mean whole blood radioactivity usually increases to a peak value by the sixth hour of 11.7% (lipid blood value, 3.7%), and then gradually declines so that after 24 hours approximately 2% (lipid blood value, 0.2%) remains. The organic fraction represents less than 50% of the total. Twenty-four-

hour urine collections contain between 20 and 40% of the administered radioactivity, and the average fecal radioactivity over this period is less than 2%.

2. *Diagnostic Evaluations:* In the differential diagnosis of steatorrhea, radioactive fat test meals are very useful.[3-7] The use of triolein alone or in combination with oleic acid leads to characteristic blood absorptive patterns which frequently suffice to establish the etiology of the derangement. On fewer occasions, fecal analyses may be necessary to complete the picture. Thus, a normal triolein curve rules out a major absorption defect, whereas

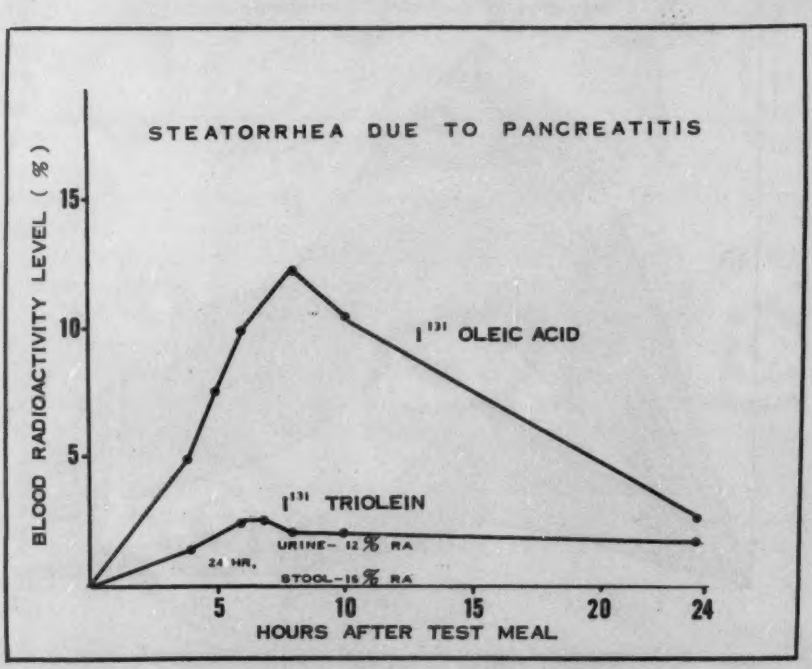

FIG. 3. Radioactive fat blood patterns in steatorrhea due to pancreatitis.

a flat curve plus an elevated stool activity is indicative of malabsorption. This may result from faulty digestion or from a primary mucosal defect. The response to an oleic acid meal may then be used to delineate this problem. A normal blood curve is evidence that pancreatic lipase is deficient (figure 3). A flat curve suggests that the error is mucosal in origin, as found in sprue (figure 4, table 2).

The test is also useful in the differential diagnosis of jaundice. A normal triolein absorption curve rules out any major obstructive process, whereas a flat response together with a normal oleic acid test is indicative of an extrahepatic block.

Figure 5 depicts the results obtained with these two labeled substances

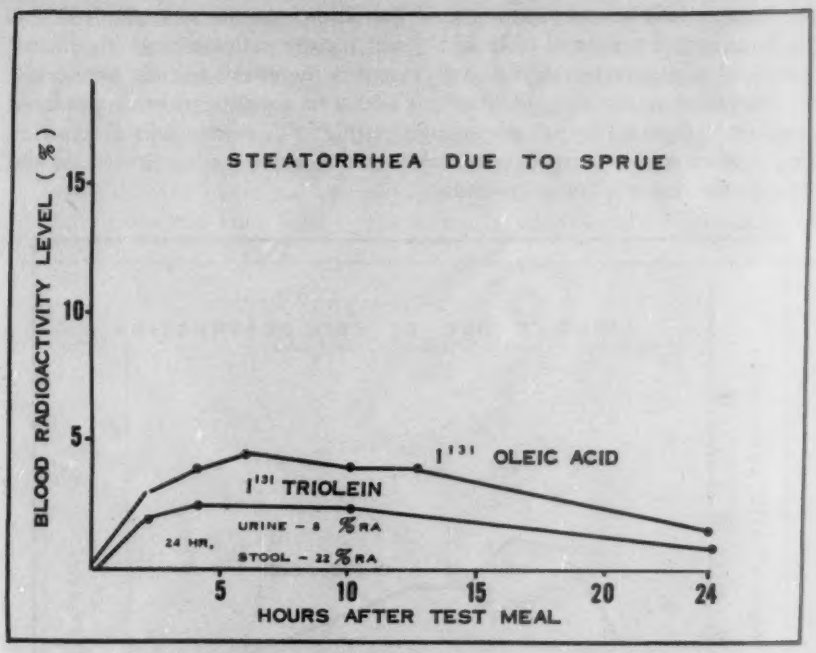

FIG. 4. Radioactive fat blood patterns in sprue.

in a 53 year old white male with jaundice of recent onset. The historical review as well as the physical examination was of minimal help in arriving at a diagnosis, and laboratory findings were conflicting. The flat triolein response with a normal oleic acid study suggested pancreatic disease, probably carcinoma of the head, as the etiology. This was confirmed at surgery.

Another example of the value of this procedure is shown in figure 6. This 45 year old female was hospitalized because of painless jaundice associated with light stools. Liver function tests were also indicative of obstructive jaundice, and surgery was contemplated. Because of two normal triolein studies, however, a conservative regimen was pursued, on which the patient completely recovered. Before discharge a history of Thorazine ingestion was obtained which adequately explained the course of events.

Although this technic appears to be of definite help in the management

TABLE 2

Interpretation of Radioactive Fat Tests in Steatorrhea

Triolein	Oleic Acid	Interpretation
Normal	Normal	Normal
Abnormal	Normal	Pancreatic
Abnormal	Abnormal	Sprue

of the jaundiced patient, certain basic limitations should be recognized. A flat triolein and a normal oleic acid result merely indicates that insufficient quantities of pancreatic enzymes are present in the intestinal tract for normal fat absorption to occur. Whether this is due to not enough being produced (pancreatic disease) or just not enough getting in (common duct obstruction with a stone and a normal pancreas) is not revealed by the procedure and must be decided on clinical grounds.

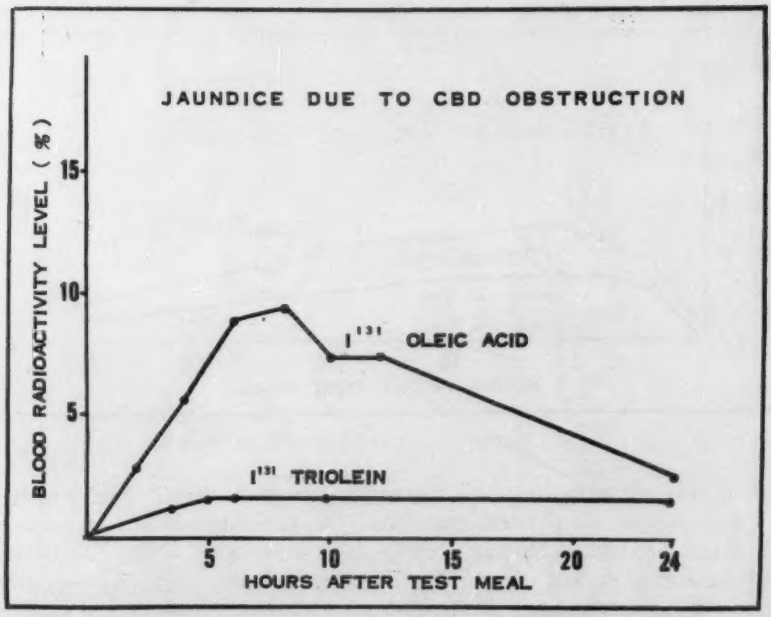

FIG. 5. Radioactive fat blood patterns in jaundice due to common bile duct obstruction.

3. *Evaluation of the Degree of Fat Malabsorption:* In certain conditions, such as regional ileitis, lymphosarcoma, Whipple's disease, a gastrocolic fistula, or following a subtotal gastrectomy, varying degrees of impaired fat absorption may be present. The radioactive fat technic affords a simple way to assay this.[8, 9]

We have also been impressed by the marked decrease in fat absorption revealed by this test in patients with heart failure, and its attendant improvement following cardiac compensation (figure 7). This may well be an important factor in the weight loss noted by many patients with chronic passive congestion. Whether this impairment results from the edema of the intestinal mucosa that is present [10] or from other factors is at present under investigation. Recent observations on the role that fat plays in cardiac muscle metabolism are also pertinent to our observations.[11]

4. *Metabolic Studies:* Another large category where labeled lipids appear to have a place is in the study of several presumably metabolic diseases, notably the essential hypercholesterolemias, coronary atherosclerosis, and perhaps obesity. We have found that in each of these conditions the radioactive fat tolerance curves demonstrated marked differences from the normals.[12] These were characterized by unusually high peak blood levels of total and lipid blood radioactivity, delays in attaining these concentrations, and elevated-24 hour values. In many, in addition, the lipid/whole blood

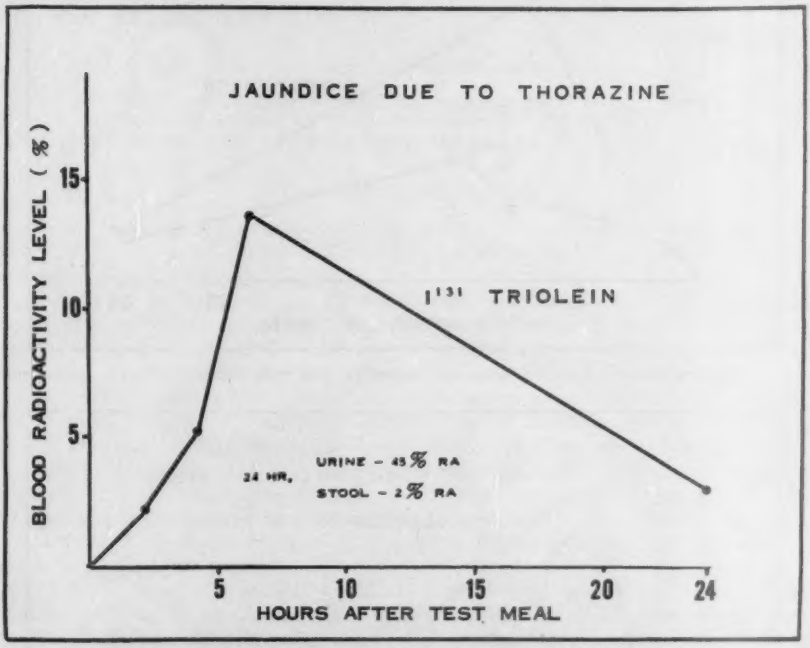

FIG. 6. Radioactive triolein absorption in jaundice due to Thorazine.

activity ratio showed that a major fraction was present in the organic portion. These results indicate that a similar error in fat metabolism exists in these different categories of patients, and point the way to further investigations.

And finally, in studies with mixed meals, isotopic fat can be administered with glucose and/or protein, and the mutual effects of one on the other can be easily measured (figure 8).

SUMMARY

Isotopically labeled fat or fatty acid is a new and effective tool that is available to the clinician in the study of various conditions associated with abnormal lipid metabolism.

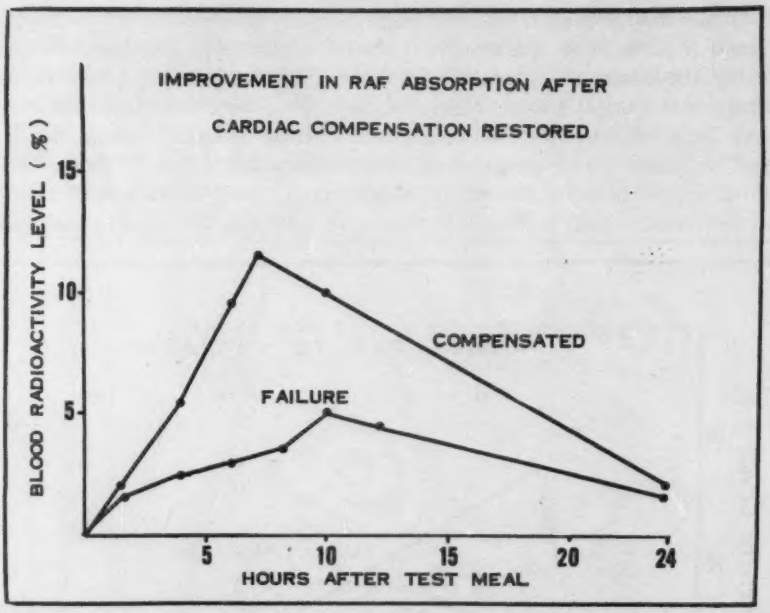

FIG. 7. Radioactive triolein absorption in congestive failure before and after compensation.

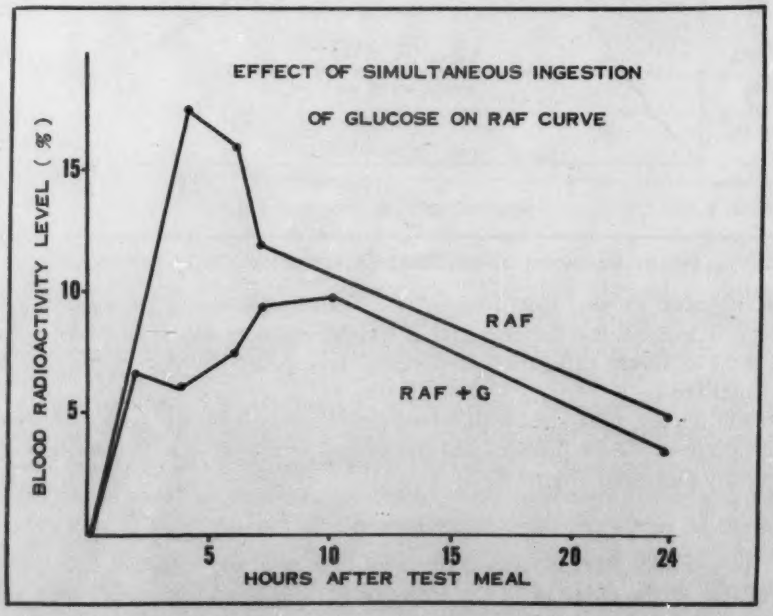

FIG. 8. Effect of simultaneous ingestion of glucose on radioactive fat absorption.

Blood absorptive patterns after an oral test meal of these substances may be used diagnostically either to determine the etiology of steatorrhea or the site of jaundice, or to evaluate the degree of fat malabsorption in regional ileitis, sprue, congestive failure and other diseases before and after treatment. In addition, tolerance tests in coronary atherosclerosis, hypercholesterolemia and obesity may be used to follow the fate of ingested fat in a much simpler and more precise manner than is now available.

It is believed that future modifications of the procedure, with extensions into wider spheres, should result in much valuable information concerned with basic metabolic mechanisms.

ACKNOWLEDGMENT

We acknowledge with thanks the invaluable assistance given by our isotope technician, Miss Hettie Brenz. In addition, Dr. J. Gershon-Cohen, the Director of the Radiology Department, has continually given us much stimulation and assistance in this undertaking.

SUMMARIO IN INTERLINGUA

Grassias e acidos grasse con marcage isotopic es un efficace addition al armamentario del clinico in studiar varie morbos que es associate con anormalitates del metabolismo de lipidos.

Le curvas del absorption de iste substantias in le sanguine post un repasto de essayo pote esser usate (1) diagnosticamente pro determinar le etiologia de steatorrhea o le sito de jalnessa o (2) clinicamente pro evalutar le grado del malabsorption de grassia in ileitis regional, sprue, disfallimento congestive, e altere conditiones—ante e post le tractamento. Assi, un normal curva de trioleina exclude le possibilitate de un major defecto de absorption, durante que un curva deprimite insimul con elevate activitate in le feces indica le presentia de malabsorption. Isto pote esser le resultato de un defecto digestive o de un primari defecto mucosal. Le responsa al ingestion de un repasto de acido oleic pote alora utilisar se pro resolver le problema. In tal casos, le presentia de un normal curva post le ingestion del agente mentionate indica carentia de lipase pancreatic. Un curva deprimite suggere le presentia de sprue.

In le diagnose differential de jalnessa, un normal curva del absorption de trioleina exclude le possibilitate que un major processo obstructive es presente, durante que un curva deprimite insimul con normalitate del test con acido oleic indica le presentia de un bloco extra-hepatic.

In plus, in casos de atherosclerosis coronari, de hypercholesterolemia, e de obesitate, grassia radio-active pote esser utilisate in sequer le destino de grassia ingerite multo plus simple- e precisemente que es nunc possibile.

Es exprimite le conviction que futur modificationes del methodologia, con applicationes de illo in plus extense campos, va resultar in le obtention de multe importante informationes con respecto al mechanismos del metabolismo basal.

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MAGNESIUM DEPLETION IN MAN*

By Russell E. Randall, Jr., Captain, USAF (MC),† Elsie C. Rossmeisl, and Kenneth H. Bleifer, Captain, USAF (MC), *Boston, Massachusetts*

The discovery of a neuromuscular disorder in animals specifically related to a deficiency of magnesium[1-9] has led to investigation of this ion in various clinical disorders in man.[10-31] Studies have been seriously handicapped by several factors. The quantitative determination of magnesium has proved troublesome, particularly with the older precipitation methods.[32-34] The current methods employing colorimetric technics,[35-37] and the newer methods employing flame photometry,[38] spectrography[39-41] and versene chelation,[42-44] are rapidly overcoming this barrier. The natural distribution of the magnesium ion has been a particularly troublesome problem. Its location chiefly within cells and bone makes difficult the interpretation of many studies concerned largely with the relatively small extracellular phase of this ion.[25, 45, 46] Renal excretion studies are complicated by the high degree of renal tubular reabsorption of magnesium[25, 47] and a filtered load which varies with the degree of binding of this ion to the serum proteins.[19, 48, 49] Variation in intestinal absorption and metabolic changes imposed by other ions and conditions have further complicated studies.[11-13, 17, 50-62]

In man, reports have dealt mainly with observations of psychiatric and neuromuscular symptoms associated with low serum magnesium concentrations.[10, 15, 16, 18, 20-28, 30, 31] The symptoms have included delirium, confusion, muscle tremors, cramps and twitchings, choreiform and athetoid movements and, rarely, convulsions. While these symptoms have in general disappeared following magnesium therapy, insufficient data have been presented to document conclusively a state of magnesium depletion causally related to the observed symptomatology. The present report includes observations in 12 patients with similar neuromuscular and psychiatric abnormalities and associated disturbances in magnesium metabolism. In 10 instances the serum magnesium concentrations were notably depressed. Balance data gave evidence for depletion of the total body magnesium in several patients, and a disordered metabolism of calcium was apparent in all. The data in three patients will be shown in detail and the pertinent features of all cases reviewed.

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From the Medical Service and Research Laboratory, Boston Veterans Administration Hospital, and the Departments of Medicine, Boston University School of Medicine and Tufts University School of Medicine, Boston, Massachusetts.

† Present address: 4167th USAF Hospital, Travis Air Force Base, California.

Requests for reprints should be addressed to Secretary, Research Laboratory, Boston Veterans Administration Hospital, 150 South Huntington Avenue, Boston 30, Massachusetts.

Methods and Materials

Hospitalized patients with a variety of clinical diagnoses from the surgical, neurologic and medical services were studied because of the sudden appearance of psychiatric and neuromuscular symptoms (table 1). The completeness with which balance data were obtained varied, but in general there was a known parenteral intake of fluids and electrolytes, daily measurements of urinary solute excretion (collected by catheter), and measurements of gastric magnesium losses when gastric drainage was employed. Accuracy of urine collections was substantiated by measurement of the daily excretion of creatinine. Fecal excretion data for magnesium were determined in only two patients. Except for case 8, no patients were eating at the time the initial serum and renal excretion values were obtained, but they were receiving fluids parenterally, which in general did not contain added magnesium or calcium.

Electroencephalograms were obtained prior to magnesium therapy in six patients (cases 2, 4, 5, 8, 9 and 10), and at varying times following therapy in four of these. Electrocardiograms were obtained in eight patients (cases 2, 4, 5, 7, 8, 10, 11 and 12). Electromyograms, using surface electrodes, were obtained before therapy in two patients (cases 4 and 10). One patient (case 11) was given 1 mg. of prostigmine intravenously with 0.06 mg. of atropine during the period of the neuromuscular disorder and was closely observed during a subsequent 80-minute period.

In general, base line serum and renal excretion values were obtained prior to any divalent electrolyte therapy. Cases 2 and 3 received infusions containing 36 and 31 mEq., respectively, of the calcium ion as calcium gluconate over three-hour periods prior to the administration of magnesium. In cases 1, 2, 3, 4, 5, 6, 10, 11 and 12, magnesium was administered intramuscularly or intravenously as magnesium sulfate,* providing 25 to 125 mEq. of magnesium daily during the initial periods of study. Cases 4, 6, 10 and 11 received no calcium during this initial period of therapy, while the subsequent infusions in cases 2, 5 and 12 contained calcium gluconate. All patients except case 8 received intravenous fluids containing sodium chloride, dextrose, parenteral vitamins (no vitamin D) and potassium (except for case 5) immediately preceding and during the periods of study. Serum electrolyte and excretion data were obtained frequently in each instance and will be mentioned below.

Serum and urine were analyzed for magnesium by the titan yellow method of Garner,[35] for calcium according to Fiske and Logan,[63] and a modification of the method of Elliott,[64] and for sodium, chloride, potassium and creatinine by methods previously described from this laboratory.[65] Phosphorus was measured by the method of Fiske and Subbarow,[66] alkaline phosphatase by that of Bodansky,[67] serum protein as by Gornall et al.,[68] and

* Magnesium sulfate as prepared by Lilly & Co.; each 2 ml. ampule of $MgSO_4 \cdot 7H_2O$ (50%) contains approximately 99 mg. (8.2 mEq.) of the magnesium ion.

carbon dioxide content by the method of Van Slyke and Neill.[69] Normal values in this laboratory for serum magnesium concentrations are 1.7 to 2.7 mEq./L., with a mean of 2.2 mEq./L., for serum calcium, 4.4 to 5.2 mEq./L., and for the serum phosphorus, 2.8 to 4.4 mg.%.

Autopsy examination was performed in cases 1, 5, 7, 10, 11 and 12, and surgical biopsies (bowel and liver) were obtained in cases 2 and 4. Tissues were stained with hematoxylin and eosin, for iron with Turnbull's blue,[70] and for calcium by von Kossa's silver stain.[71]

Results and Case Reports

Table 1 depicts the basic clinical and initial laboratory data in all 12 patients studied. The case reports of three of these patients (cases 2, 4 and 5) are presented below, with their individual laboratory data depicted in tables 2, 3 and 4. The pertinent clinical, laboratory and special test data in all patients are summarized below under individual headings.

Case Reports

Case 2. A 68 year old white male underwent a Miles' abdominoperineal resection with sigmoid colostomy in 1950 for adenocarcinoma of the rectum. In February and July, 1955, two courses of 250 K.V. x-ray therapy (1,900 and 2,000 r, tumor dose) were administered through a single posterior portal (10 by 15 cm.) to an area of metastasis appearing over the sacrum. Because of continued localized sacral pain, an additional 4,000 r tumor dose was administered in November, 1955, from a 2 million volt x-ray machine through anterior and posterior pelvic portals (12 by 18 cm.). Following the latter irradiation there was relief of pain, but a large ulcer developed over the sacrum which later showed carcinoma on biopsy. Frequent bulky, foul-smelling stools began promptly after the final irradiation, with intermittent episodes of severe, watery diarrhea. This pattern continued for over a year, and in March, 1957, the patient was hospitalized because of fecal drainage from the base of the large sacral ulcer. Except for marked cachexia, physical examination was unremarkable. Abdominal exploration revealed marked abnormality of the entire small bowel, with multiple adhesions binding together a shortened, stiff, small intestine. The serosa was thickened. The mesentery appeared to be shortened and showed extensive capillary injection. A fistula between a loop of ileum and the sacral ulcer was excised. This showed poorly differentiated adenocarcinoma in the sacral portion, but no tumor tissue was identified within the peritoneal cavity. One foot of ileum was removed, and an end-to-end ileoileostomy was performed. Microscopic examination (figures 1 and 2) of the ileum showed a serosa thickened by dense fibrous connective tissue, a prominent muscular layer, and numerous engorged blood vessels. The submucosa was edematous and the mucosa markedly atrophic, with shortened, club-shaped villi, vacuolization, and areas completely denuded of epithelial lining. In addition, a few scattered lymphocytes were noted, in both the mucosa and the submucosa.

Postoperatively the patient did well except for the resumption of frequent loose, bulky stools. X-rays revealed pulmonary emphysema and marked demineralization of the lumbosacral spine and pelvis, without evidence of metastases or pseudofractures. Diarrhea, anorexia and weight loss continued at home, and because of increasing weakness and episodes of bizarre behavior the patient was again hospitalized on

TABLE 1

Clinical and Laboratory Data in All Patients

Patient	Diagnosis	Age	Symptoms	Serum*										Urine†			Clinical Response to Mg Therapy	% Magnesium Retained‡
				Mg† mEq./L.	Ca† mEq./L.	P† mg.%	Alk. P'tase B.U.	A/G gm.%	Na mEq./L.	K mEq./L.	Cl mEq./L.	CO_2 mM./L.	Cr mg.%	Mg mEq./24 hrs.	Ca mEq./24 hrs.	P gm./24 hrs.		
1	Alcoholism and cirrhosis; perforated duod. ulcer	60	Delirium, twitchings	1.3	3.4	3.5	2.5	1.8/3.6	134	4.5		19	2.3				Improved	91%
2	Malabsorption, metastatic carcinoma of rectum	68	Delirium, twitchings, rigidity	0.4	2.2	3.3	2.0	3.5/1.0	132	3.0	100	20	0.7	0	<1		Improved	76%
3	Carcinoma of mouth	68	Confusion, twitchings	0.9	4.1	2.5	2.3		122	4.1			0.7	2	6	.37	Improved	
4	Alcoholism and cirrhosis, colectomy (polyps)	63	Delirium, twitchings	1.5	3.9	1.7	2.5	1.8/2.3	136	3.7	96	24	0.8	2	<1	.01	Improved	44%
5	Cerebral thrombosis, status epilepticus, diabetes mellitus	38	Status epilepticus	0.4	2.8	2.1	20.0	2.5/3.4	139	2.3	80	42	0.7	21	<1	.31	Improved with Mg, Ca and K	40%
6	Alcoholism and cirrhosis, chronic pancreatitis, delirium tremens, severe malnutrition	41	Delirium, tremors, twitchings	1.1	3.4	1.6	13.1§	1.8/2.0	133	3.3	102	20	0.4	<1	<1	.01	No *immediate* change	6%

* All serum and urine values were obtained immediately preceding the administration of either magnesium or calcium salts.

† Normal values in this laboratory for the serum magnesium at 1.7 to 2.7 mEq./L.; for calcium, 4.4 to 5.2 mEq./L., and for phosphorus, 2.8 to 4.4 mg.%.

‡ Retention refers to the per cent of the administered magnesium ion *not* recovered in the urine or gastric drainage during the initial periods (24 to 72 hrs.) of intravenous or intramuscular magnesium sulfate therapy.

§ These values were associated with elevated serum bilirubin values.

TABLE 1—*Continued*

Patient	Diagnosis	Age	Symptoms	Serum*										Urine†			Clinical Response to Mg Therapy	% Magnesium Retained‡
				Mg† mEq./L.	Ca† mEq./L.	P† mg.%	Alk. P'tase B.U.	A/G gm.%	Na mEq./L.	K mEq./L.	Cl mEq./L.	CO_2 mM./L.	Cr mg.%	Mg mEq./24 hrs.	Ca mEq./24 hrs.	P gm./24 hrs.		
7	Chronic glomerulonephritis	40	Confusion, twitchings	0.8	3.8	10.1	4.3		133	3.8	76	23	17.3	1	3		Improved with oral feeding	
8	Alcoholism and cirrhosis	60	Confusion, tremor, cerebellar symptoms	1.2	4.3	2.8	4.8	3.8/3.4	132	4.5			1.1	3	2		Improved with oral feeding	
9	Old subarachnoid hemorrhage	51	Stupor, unilateral myoclonic jerks and tremor	1.1	3.3	3.0	5.0		142	2.6	82	18	0.4	<1	1	.06	Slight improvement	
10	Alcoholism and cirrhosis, Wernicke's syndrome, delirium tremens	32	Delirium, tremors, twitchings	3.0	3.8	3.8	6.1§	3.2/2.9	134	3.2	81	30	1.7	0	0	.69	Sedation only	46%
11	Alcoholism, carcinoma of ureter with anuria	67	Delirium, twichings	1.9	4.3	3.8	3.0	3.6/2.9	140	4.7	102	23	2.0	2	<1	.40	Improved	60%
12	Carcinoma of stomach, total gastrectomy, chronic pancreatitis	63	Delirium, twitchings, tremors, athetosis, rigidity	0.9	3.2	1.0	14	2.6/2.0	120	4.1	90	21	0.3	12‖	7‖	.01	Improved	

‖ Collection period was preceded by the administration of calcium (intravenously) and tube feedings.

TABLE 2

Clinical and Laboratory Data in Case 2

Date	Serum*					Blood	Urine			Tests	Treatment				Symptoms and Remarks
	Mg mEq./L.	Ca mEq./L.	P mg.%	Alk. P'tase B.U.	A/G gm.%	Hgb. gm.%	Mg mEq. 24 hrs.	Ca mEq. 24 hrs.	P gm. 24 hrs.		Magnesium	Calcium	Vit. D	Other	
1957 May 6			4.0			13								I.V. fluids with K, Na and vitamins	Diarrhea, delirium
May 14–15	0.4	2.2	3.3	2.0	3.5/1.0		0	<1	.40					Same	Delirium, twitchings
May 16										EEG abnormal ECG abnormal		36 mEq. I.V.		Same	No change
May 17–20							36†	35†			150 mEq.† I.V.	54 mEq.† I.V. 60 mEq. p.o./day	50,000 u. daily	Normal diet	Dramatic improvement in all symptoms
May 20	1.7	3.4	3.0	3.0						EEG abnormal ECG abnormal		60 mEq. p.o./day	100,000 u.	Same	No psychosis, no twitching, moderate diarrhea
June 5	0.8	3.8	3.0				<1	<1		Abnormal G.I. series, xylose tolerance, serum carotene and stool fat excretion		0	Same	Same	Improved
June 28	0.4	2.3	3.1	2.0	1.8/2.7							60 mEq. p.o./day	Same	Same	Same
July 30	0.5	3.6	2.9	2.2		9	0	<1	.65	EEG improved ECG improved		Same	300,000 u. daily	Added protein, atropine and opiates	Less diarrhea
Aug. 29	1.5	4.9	3.0	2.1	2.8/3.5		0	<1	.55	Positive magnesium balance		Same	Same	Same	Same
Nov. 18	1.2	3.6	2.9	4.3	3.1/2.1	9	0	<1	.28			Same	Same	Same	
1958 Feb. 17–21	1.3	3.6	3.0	6.5	1.9/2.9	9	0	<1	.28	Positive magnesium and calcium balance		None	None	Normal diet	X-ray: lung metastases
	2.8	3.9	2.5	7.0							58 mEq. I.M. "test"				

* There were no abnormalities or significant changes in the serum concentrations of sodium, potassium, chloride, carbon dioxide content or creatinine.
† Total values for the 72-hour period indicated.

TABLE 3

Clinical and Laboratory Data in Case 4

Date	Serum*					Urine			Gastric	Tests	Treatment		Symptoms and Remarks
	Mg mEq./L.	Ca mEq./L.	P mg.%	Alk. P'tase B.U.	A./G. gm.%	Mg mEq. 24 hrs.	Ca mEq. 24 hrs.	P gm. 24 hrs.	Mg mEq. 24 hrs.		Magnesium	Other	
1957 Aug. 5				8.0	2.3/2.3					Abnormal hepatic function		Improved diet and vitamin intake	
Sept. 5			4.4	4.5	3.1/3.0							I.V. dextrose, water, saline, potassium, vitamins	Partial colectomy
Sept. 9	1.5	4.8	2.1	2.6								Same	Delirium, diarrhea
Sept. 12	1.6	3.9	1.5	2.5	1.8/2.3	2	<1	.01	<1	EMG abnormal EEG abnormal ECG abnormal Serum creatine 1.1 mg.%		Same	Delirium, twitchings
Sept. 13 (15 hrs.)						42†	10	.01	3		108 mEq. I.V.	Same	
Sept. 14 (24 hrs.)	3.5	4.2	3.0	3.7		57†	4	.02	<1	EEG improved ECG improved	75 mEq. I.V.	Same	Clearer mentally, no twitching
Sept. 15 and 16 (48 hrs.)						82†	3	.06	3	EEG improved	86 mEq. I.V.	Same	Same
Sept. 17	2.3	3.5	3.2	3.6								Same	Same
Sept. 18	1.4	3.8	3.4	4.9		6	2	.12				Same	Minor confusion, occasional twitch
Oct. 18	1.2					6	2	.45			25 mEq. I.V. daily, then normal diet	Oral feedings	No symptoms
Nov. 18	2.2	4.8	4.3		3.4/4.0	8	2	.30		Serum creatine 0.3 mg.%		Same	Home

* There were no abnormalities or significant change in the concentrations of serum sodium, potassium, chloride, carbon dioxide content, creatinine or blood hemoglobin.
† Total values for the periods specified.

TABLE 4

Clinical and Laboratory Data in Case 5

Date	Serum										Blood	Urine			Tests	Treatment	Symptoms and Remarks
	Mg mEq./L.	Ca mEq./L.	P mg.%	Alk. P'tase B.U.	A/G gm.%	Cr mg.%	Na mEq./L.	K mEq./L.	Cl mEq./L.	CO_2 mEq./L.	Hgb. gm.%	Mg mEq./24 hrs.	Ca mEq./24 hrs.	P gm./24 hrs.			
1957 May 12–21					4.1/2.5	0.8				25	12				EEG abnormal ECG abnormal	I.V. fluids (no potassium)	Hemiparesis, focal to grand mal epilepsy to status epilepticus
June 5	0.4	2.8	2.1	20.0	2.5/3.4	0.7	139	2.3	80	42		21	<1	.30	Arterial pH, 7.53, serum carotene, 0		Status epilepticus
June 6–7	1.5	3.6	1.1	21.0		0.7	133	2.7	79	43		See text				I.V. magnesium, calcium and potassium*	Only focal seizures
June 11–14	1.6	4.4	3.6	20.0		0.7	131	4.2	88	36	11	See text				Oral calcium and feedings, I.M. magnesium sulfate*	Rare focal seizures, speech improved
June 17	1.1	4.5	4.2					4.3	93	30		<1	4	.45	Normal GI series, serum carotene and xylose tolerance	Oral calcium and feedings only	Same
June 20–24	1.0	4.6	4.6		2.5/3.4				94	28	10	48†	See text		EEG improved, ECG improved, positive magnesium balance	167 mEq. magnesium I.M.†	No seizures; hemiparesis remains; walking
July 30	1.2	4.5	4.5	9.4	3.2/3.1		134	4.9	84	22		<1	<1	.36	EEG improved	Normal diet	Myocardial infarct; died Aug. 10

* See written case report for dosage.
† Total values for the 96-hour period indicated.

FIG. 1. From the ileum (case 2), showing marked edema of the mucosa and submucosa, with scattered round cell infiltration, marked atrophy of villi, and absence of surface epithelium.

FIG. 2. From another segment of the ileum (case 2), showing marked vacuolation of the epithelium lining the villi, which display variations in architectural pattern and increased secretory activity, resulting in large pools of mucinoid material.

May 6, 1957. At this time cachexia and the sacral ulcer were the only remarkable physical findings, and the neurologic and psychiatric examinations were normal.

On the second hospital day the patient suddenly became irrational, disoriented, confused, and progressively noisy, combative and wildly restless, requiring constant restraints. He experienced hallucinations, but demonstrated no other neurologic abnormalities. He was given intravenous fluids containing vitamins, dextrose, saline and potassium. The severe psychosis persisted for six days, when a severe neuromuscular disorder developed, characterized by muscular rigidity and cogwheeling, coarse tremor, opisthotonos, extensive fine muscle fasciculations, and twitching of large and small muscle groups. There were no other detectable neurologic abnormalities, and Chvostek's and Trousseau's tests were negative.

After discovery of the marked depressions in the serum concentrations of calcium and magnesium (table 2), 18 mEq. of calcium as calcium gluconate were infused during a one-hour period and followed by a similar infusion during three additional hours. This caused no clinical improvement, and may have been associated with further deterioration. Electroencephalography showed a diffusely abnormal pattern, with generalized slow-wave activity and low voltage (figure 3). Electrocardiography showed a nodal rhythm, slight prolongation of the QT interval, and nonspecific depressions of the ST segments and T wave voltage. Both tracings were repeated immediately after the calcium infusion and showed no significant change.

Magnesium sulfate was then (May 16) added to the intravenous fluids, and during the subsequent three-day collection period, 150 mEq. were given (in addition to the magnesium contained in the diet begun on May 18). Intravenous calcium administration was continued. Eighteen hours following the initial dose of intravenous magnesium sulfate (50 mEq.) the patient was remarkably rational, oriented, and completely free of the previous neuromuscular disorder. By the third day of therapy he was up and about, completely transformed from his "terminal" state into a delightful elderly man, manifesting no psychiatric or neuromuscular abnormalities.

The renal excretion of magnesium during the three-day period of magnesium administration represented only 24% of the intravenous dose. This low value occurred despite an additional unmeasured oral intake of magnesium and simultaneous oral and intravenous calcium administration. Retention of *at least* 76% of the administered dose of magnesium can be assumed for this period.

Six days following the onset of magnesium therapy (May 22), and at a time of improvement in the serum magnesium and calcium values as well as in his clinical state, the electroencephalogram and electrocardiogram failed to show reversion toward normal (figure 3).

Vitamin D and calcium lactate were then added to his dietary regimen (table 2), as well as multivitamins, protein supplements, deodorized tincture of opium and tincture of belladonna. The frequency of the bowel movements decreased, but the stools remained bulky and greasy. Documentation of intestinal malabsorption was obtained by several tests: (1) x-rays of the gastrointestinal tract showed a shortened ileum lying mainly within the pelvic area, with irregular clumping and segmentation; (2) microscopic stool examination showed increased amounts of undigested muscle fibers but no increased fat when heated with Sudan III and acetic acid; (3) three-day stool fat excretion represented 30% of the oral intake (normal, under 10%); (4) the serum carotene level was 40γ% (normal, over 50γ%); (5) a xylose tolerance test [72] was markedly abnormal, with a two-hour blood level of 17 mg.% and only 1.8 gm. of the 25-gm. oral dose appearing in the five-hour urine collection. The serum iron concentration was later 36μ%. A normocytic anemia developed which failed to respond to injections of vitamin B_{12}, oral folic acid, and oral ferrous gluconate administration.

The subsequent clinical course is of importance. With no additional administra-

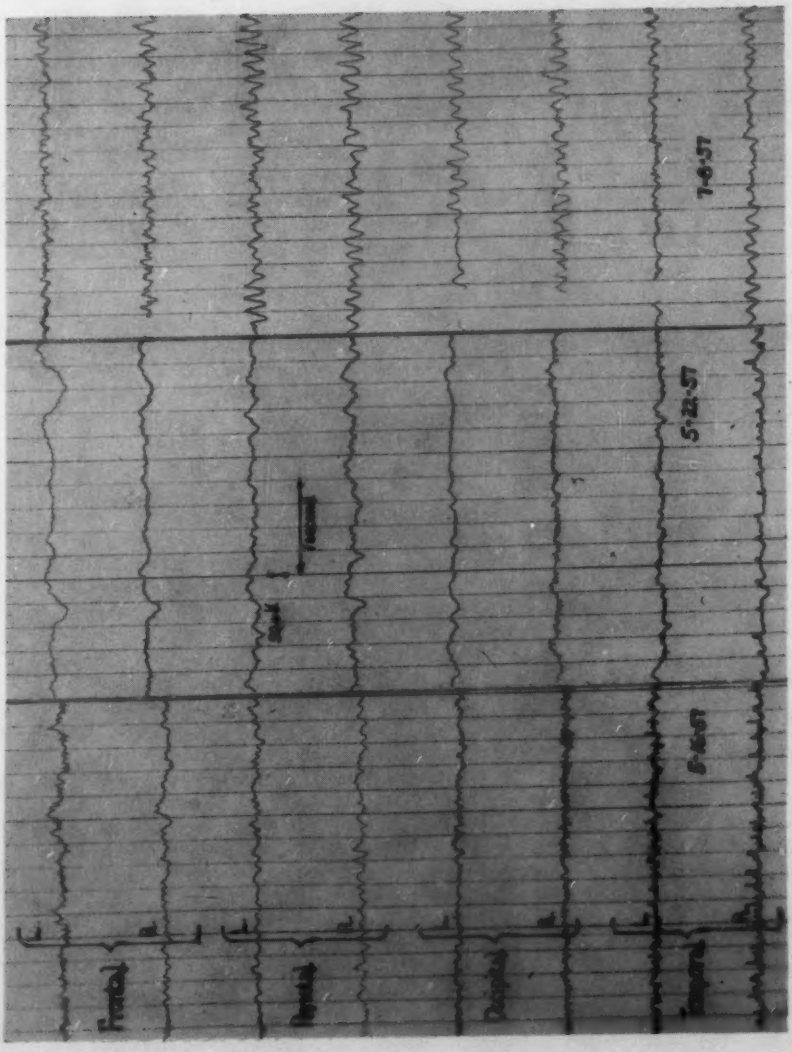

FIG. 3. Serial electroencephalograms in case 2, showing generalized low voltage and slow wave activity on May 16 and May 22, 1957, followed by an improvement on July 8, 1957, with the appearance of normal alpha rhythm.

tion of magnesium salts, and continuing diarrhea, both the serum magnesium and calcium fell progressively to levels (June 28) almost identical to those recorded previously (May 14). At this time there were *no* psychiatric or neuromuscular symptoms. Neurologic examination, including Chvostek's and Trousseau's tests, was normal. Renal excretion data continued to show marked conservation of magnesium and calcium. The electroencephalogram was now (June 28) considerably improved, showing greater amplitude and a normal frequency and rhythm (figure 3). Electrocardiography showed a sinus rhythm, a shorter QT interval, and improved T wave amplitude.

With more intensive treatment with vitamin D, folic acid, ferrous gluconate, oral protein supplements and agents to decrease the bowel motility, there was an associated improvement in the serum concentrations of magnesium and calcium. In August, 1957, and February, 1958, two three-day balance studies demonstrated marked renal conservation of magnesium and calcium. Fecal magnesium excretion was observed to vary markedly according to the nature of the stool pattern. Episodes of severe diarrhea were occasionally associated with a slightly negative magnesium balance by virtue of the fecal losses, but with control of the bowel movements a positive over-all balance for calcium and magnesium was repeatedly observed. Eighty-nine per cent of an injected 58 mEq. of magnesium sulfate (seven doses) was retained over a 48-hour period in February, 1958. The patient remained relatively symptom-free until March, 1958, since which time he has shown increasing weakness, weight loss, and x-ray evidence of pulmonary metastases.

Comment: Severe intestinal malabsorption of numerous dietary constituents occurred in an elderly patient with carcinomatosis. Extensive post-irradiation changes[73, 74] of the small bowel were considered to be etiologic in the disordered gastrointestinal function. While temporary disturbances in absorption have been reported following smaller doses of x-irradiation,[74] such prolonged malabsorption has not been previously reported. Severe psychiatric and neuromuscular symptoms (delirium, tremors, twitching and opisthotonos) appeared suddenly, were associated with marked depressions of the serum concentrations of magnesium and calcium, and disappeared dramatically following magnesium administration without response to intravenous calcium administration. Symptoms did not reappear despite subsequent decreases in the concentration of the serum magnesium to 0.4 mEq./L. and the serum calcium to 2.3 mEq./L. Marked retention of magnesium given intravenously to this patient and of magnesium contained within the diet is believed to reflect a marked depletion of the total body magnesium, presumably produced by excessive fecal losses.

Abnormal electroencephalograms and electrocardiograms improved slowly following therapy, apparently independent of serum electrolyte concentrations and clinical symptoms.

Case 4. A 63 year old white male, a chronic alcoholic, was hospitalized on August 5, 1957, because of six months of anorexia, intermittent vomiting, and a 34-pound weight loss. Physical examination revealed cheilosis, a smooth tongue, hepatomegaly, and evidence of peripheral neuropathy. Blood examination initially showed a serum albumin of 2.3 gm.%; globulin, 3.3 gm.%; alkaline phosphatase, 8.0 Bodansky units; cephalin flocculation, 3 plus in 48 hours; serum bilirubin, 0.6 mg.%; serum cholesterol, 148 mg.%, with 47 mg.% as cholesterol esters. The

prothrombin time was 100%, and the bromsulfalein retention was 24% in 45 minutes. The serologic test for syphilis (VDRL) was negative.

Multiple polyps in the transverse and descending colon were discovered, and after five weeks of improved food and vitamin intake and a seven-pound weight gain a partial colectomy was performed on September 5, 1957. Except for multiple benign polyps, the large and small bowel appeared to be normal grossly, and microscopic examination of the resected colon was not remarkable. Liver biopsy revealed early cirrhosis and extensive hemosiderosis.

Postoperatively, large amounts of dextrose and sodium and potassium chloride were administered to replace copious amounts of gastric and fecal losses of fluid. Mild confusion on the second postoperative day progressed to a severe psychosis by the fourth day, which was characterized by hallucinations and wild, combative behavior. This mental state persisted for three additional days, during which time the large fluid exchanges continued. The patient then developed, in addition, generalized fine muscle twitchings and choreiform movements produced by twitchings of larger muscle groups. Analyses of blood and excreta at that time are shown in table 3. Electromyography, using surface electrodes, demonstrated widespread asynchronous bursts of activity (single or double spikes), as well as rhythmic (eight per second) discharges of complex bursts. Electroencephalography showed only diffuse low voltage and slow wave activity. The previously normal electrocardiogram (August 12, 1957) was now replaced by one characterized by generalized T wave lowering and auricular and ventricular irritability.

The addition of magnesium sulfate to the intravenous fluids, as shown in table 3, represented the only change in therapy. At the termination of the initial dose of magnesium (15 hours) the twitchings were absent and the patient was quieter and more coöperative. This improvement continued during the periods of magnesium administration and when (September 17, 1957) the serum magnesium was normal. Temporary cessation of magnesium administration was associated with a fall in the serum concentration of magnesium and a return of the psychiatric and neuromuscular symptoms, albeit less severe. Clinical improvement again followed the re-institution of magnesium sulfate administration and persisted despite the low serum magnesium values obtained on October 18.

As seen in tables 1 and 3, 44% of the infused magnesium ion was retained during the initial 39 hours of magnesium therapy, and 30% of the total dose was retained over an 87-hour period. Unmeasured fecal losses were not accounted for.

Following the administration of magnesium sulfate intravenously, slight increments in the serum concentrations of calcium, phosphorus and alkaline phosphatase occurred (table 3), as well as a significant increase in the renal excretion of calcium. A fall in these serum concentrations had been observed immediately prior to the onset of symptoms.

Repeated electroencephalography following magnesium therapy (September 14 and 16) again showed low voltage, but no slow wave activity and more alpha rhythm, thus making the tracing more nearly normal. Slight but definite improvement in the T wave voltage of the electrocardiogram had also appeared since the tracing taken two days previously.

One month following the patient's discharge from the hospital, the serum magnesium, calcium and phosphorus concentrations were normal and the serum iron was 150μ%. The patient has remained mentally clear, neurologically intact, and essentially asymptomatic.

Comment: An acute delirium preceded a neuromuscular disorder (twitchings and tremors) in a postoperative chronic alcoholic patient receiving intravenous feedings to replace copious gastric and fecal losses of fluid. The abnormal symptoms and abnormalities of the electromyogram, electroen-

cephalogram and electrocardiogram disappeared following magnesium administration. A large amount of the administered magnesium was retained.

Case 5. A 38 year old white male laborer was hospitalized on May 11, 1957, because of right hemiparesis and expressive aphasia of one day's duration. He had had known mild diabetes mellitus for five years, and the urinary findings of mild chronic pyelonephritis. No other neurologic or gastrointestinal symptoms preceded the sudden onset of the neurologic symptoms mentioned above. The diet was considered to have been adequate. Physical examination revealed only the spastic right hemiparesis, expressive aphasia, and a rectal temperature of 101°F. The initial laboratory data (May 12) were not remarkable, although there was moderate pyuria and cylindruria, and a urine culture grew *Aerobacter aerogenes.*

On the third hospital day (May 13) focal seizures originating in the right face and hand progressed to grand mal seizures, which within two days occurred as frequently as 15 to 20 times a day. This frequency increased still further to produce numerous episodes of status epilepticus daily during the following two weeks despite large doses of Dilantin and phenobarbital. No abnormalities could be detected in x-rays of the chest, pelvis, spine, long bones and skull, in a left carotid arteriogram, a pneumoencephalogram, or in several lumbar punctures (cerebrospinal fluid protein, cell count, serology, culture and India-ink examination). Electroencephalography showed low voltage and a diffuse, irregular, slow wave pattern with a left central-temporal focus of discharge, which progressed to a generalized seizure pattern with convulsive episodes. An electrocardiogram on the first hospital day revealed a normal QT interval, nonspecific ST segment depressions and T wave lowering in all leads. During the first two weeks further T wave flattening and sagging of the ST segments occurred, along with the appearance of prominent precordial U waves.

During the three weeks of severe seizure activity, fluid balance and good diabetic control were maintained by parenteral administration of dextrose, saline and crystalline insulin. No potassium was given. Large doses of penicillin and streptomycin failed to alter the clinical course. A markedly positive Trousseau's test on June 5, 1957, led to the discovery of the extreme abnormalities in the serum chemistries (table 4). Serum drawn at an earlier date (May 29) for viral studies was later analyzed and showed similar abnormalities (magnesium, 0.8 mEq./L.; calcium, 2.8 mEq./L.; phosphorus, 2.4 mg.%; alkaline phosphatase, 12 Bodansky units). The serum magnesium, calcium and phosphorus were thus already low. The hypokalemic alkalosis was believed to have resulted from a lack of potassium intake in the presence of normal or slightly increased renal losses of potassium (26 mEq./day). Intense and repeated historical investigation failed to bring out any symptoms suggestive of intestinal malabsorption. Studies of intestinal function (small bowel x-rays, xylose tolerance test, repeated serum carotene values, and stool fat excretion) likewise failed to implicate the gastrointestinal tract in producing the observed "chemical osteomalacia."[75] A surprising observation was the excessive renal excretion of magnesium occurring in the control period (June 5), in the presence of marked depressions in the serum magnesium concentration (table 4).

The apparently critical state of the patient made necessary the rapid administration of large amounts of several electrolytes. Calcium (27 mEq.), magnesium (33 mEq.) and potassium (60 mEq.) were infused during the first 16-hour period, and during the ensuing four days 18 to 20 mEq. of calcium, 50 to 62 mEq. of magnesium, and 60 mEq. of potassium were infused daily. During the first hour of electrolyte "replacement" the status epilepticus stopped and only focal seizures occurred. Within days the patient was able to carry on a conversation, and over the ensuing weeks he progressed rapidly to full ambulation, still, however, showing a residual right hemiparesis and speech defect.

The complexities of electrolyte therapy and excretion data prohibit detailed representation in table 4, but several general observations should be mentioned. While approximately 40% of the initial dose of magnesium ion was retained within the first 40-hour period, this was followed by three days of marked renal losses of magnesium (twice the parenteral intake of 50 mEq. daily). This occurred in the presence of the continuing hypokalemic alkalosis. With the gradual correction of this condition and cessation of the status epilepticus, marked retention (40%) of intramuscularly administered magnesium occurred at a later date (June 11 through 14, and June 20 through 24). Large retention (over 90%) of the magnesium contained within his diet was also noted (June 17 and July 30). Despite a constant dietary intake of calcium, both courses of intramuscular magnesium sulfate produced increased renal calcium excretion. Renal function studies performed after correction of the hypokalemia revealed a creatinine clearance of 96 ml./min., a 15-minute phenolsulfonphthalein excretion of 21%, and a maximal urinary concentration (following the injection of Pitressin) of 400 milliosmols/Kg.

One month following cessation of specific electrolyte therapy (July 30), and while the patient was receiving a normal diet, the serum calcium and phosphorus remained normal but the alkaline phosphatase was slightly elevated. The serum magnesium concentration was slightly low, and renal conservation of calcium and magnesium persisted. Electroencephalograms on June 24 and July 9 were decidedly improved, although the generalized low voltage persisted, as did the left-sided focus of abnormal activity. The pattern showed further improvement on July 27. The previously mentioned electrocardiographic abnormalities showed a progressive return toward normal following treatment.

An anterior wall myocardial infarction, occurring on July 30, 1957, was followed by a progressive downhill course, hypotension, signs of generalized cerebral insufficiency, and death on August 10, 1957.

Autopsy Findings: Cardiovascular: Generalized coronary artery atherosclerosis was observed with myocardial fibrosis and a thrombosis of the left coronary artery with an associated apical myocardial infarction. The aorta was markedly sclerotic, with extensive atheroma and calcifications. Kidneys: Acute and chronic pyelonephritis was present, with moderate arteriosclerosis of the renal vessels and occasional glomeruli showing a nodular form of interstitial glomerulosclerosis. Brain: Moderate atherosclerosis was seen throughout the cerebral arteries. A thrombosis of a branch of the left middle cerebral artery had produced infarction of a portion of the left cerebral cortex. In addition, diffuse patchy neuronal degeneration was apparent throughout the brain, plus "ballooning" of the glial cells of the deeper layers. No abnormalities could be detected in the gross or microscopic examination of the gastrointestinal tract, bone, thyroid, parathyroid glands, adrenals, pancreas or other tissues.

Comment: A diabetic patient developed severe and prolonged epilepsy following a cerebral thrombosis. Pronounced depressions of the serum calcium and phosphorus with elevations of the alkaline phosphatase were discovered, associated with marked hypomagnesemia and a hypokalemic alkalosis. Excessive renal excretion of magnesium seemed to relate best to a state of potassium depletion. Marked retention of administered magnesium was subsequently observed, probably reflecting a large depletion of total body magnesium. Clinical improvement followed therapy with magnesium, calcium and potassium salts. Abnormal electroencephalograms and electrocardiograms improved following therapy. While the precise etiology of

the electrolyte disorder remains obscure, the potassium depletion is presumed to have resulted from renal losses in the absence of an intake of potassium. A "functional" renal tubular defect, possibly related to potassium depletion, might explain the "renal wasting" of magnesium and magnesium depletion. The marked abnormalities of calcium metabolism remain most obscure. Normal serum calcium and phosphorus concentrations were maintained following control of the epilepsy and correction of the depletion of potassium and magnesium.

Summary of Observations in All Patients

Diagnoses and other Metabolic Factors: All patients were severely malnourished as a result of a variety of illnesses. Each had experienced a decreased intake of food, either as a result of anorexia (cases 2, 4, 7, 11 and 12), an inability to eat or retain food (cases 1, 3, 5, 9 and 12), or as a result of severe alcoholism (cases 1, 4, 6, 8, 10 and 11). Acute or chronic diarrhea preceded the onset of the witnessed neuromuscular disorder in seven patients (cases 2, 4, 6, 7, 9, 10 and 12), and gastric losses of fluid occurred in an equal number (cases 1, 4, 6, 7, 9, 10 and 12). Hypokalemia was or had been present in cases 5, 6 and 9, and cases 3 and 12 initially had hyponatremia.

All patients except case 8 were receiving feedings parenterally when symptoms developed or worsened. This included dextrose, saline, vitamins, and usually potassium chloride (except for case 5). Case 3 had lived on a diet relatively high in calcium and low in magnesium (milk products),[76] whereas case 7 had been receiving occasional doses of calcium gluconate in his intravenous feedings.

Symptoms and Signs: All patients were selected for study because of coexisting mental and neuromuscular abnormalities. Sudden onset of severe psychotic symptoms (delirium, hallucinations, delusions and wild, combative behavior) was present in seven patients, while mild confusion and disorientation characterized four other patients (table 1). In five of the six alcoholic patients (cases 1, 6, 8, 10 and 11), withdrawal from alcohol intake *might* have occurred immediately prior to hospitalization, but this was unlikely in two instances (cases 1 and 11). Mental symptoms *preceded* the neuromuscular symptoms by from three to six days in the eight patients (cases 1, 2, 3, 4, 7, 9, 11 and 12) in whom this relationship could be discerned.

Abnormal neuromuscular activity was characterized chiefly by twitchings. These occurred in every patient (except case 5), were generally widespread, involving large and small muscle groups, and occasionally produced choreiform movements. Athetoid movements were observed only in case 12. Muscle fasciculations were common. A rhythmic tremor was apparent in six instances (cases 2, 4, 6, 8, 10 and 12), and rhythmic unilateral myoclonic jerks occurred in one patient (case 9). Seizures occurred

in two patients (cases 5 and 7). Only one patient (case 5) demonstrated a positive Trousseau's and Chvostek's test.

Intravenous prostigmine administration in case 11 was associated with an increase in the muscle twitchings and the appearance of extensive muscle fasciculations.

Serum Electrolytes (*table 1*): Ten patients had moderate to pronounced depressions of the serum magnesium concentration. Two patients (cases 10 and 11) had symptoms identical to those observed in the other patients and balance data suggesting a state of magnesium depletion despite normal serum magnesium concentrations. Hypocalcemia of a moderate to a marked degree was present in all 12 patients. Depression of the serum phosphorus was also common, while the other serum electrolytes showed no consistent abnormality.

Retention of Magnesium: Nine patients were initially excreting significantly small amounts of magnesium in the urine during or immediately following periods of marked reduction in the oral intake of food. Abnormally large retention of magnesium contained in the diet occurred subsequently in six patients (cases 2, 3, 5, 6, 7 and 8) while parenterally administered magnesium was retained excessively in six instances (table 1). Excretion data to establish such a retention were not obtained in cases 9 and 12. Cases 10 and 11 retained significant amounts of parenterally administered magnesium despite normal serum levels of magnesium. The retentions in cases 1 and 11 occurred nine days following oliguric episodes (due to hypotension and ureteral obstruction, respectively), but during periods of large daily urine excretion (2 L. daily) and falling serum creatinine levels.

Case 5 initially demonstrated excessive renal excretion of magnesium in the presence of markedly reduced serum concentrations of magnesium, while failure to retain the initial parenteral dose of magnesium was observed in cases 5 and 6. Hypokalemia had been recently corrected in case 6, but was still present in case 5 at the time of this "wasting," and both patients subsequently demonstrated excessive retention of magnesium (oral and parenteral intake) *after* correction of the potassium depletion and the attainment of an improved state of nutrition.

Clinical Response to Magnesium Therapy: Cessation of the psychotic and neuromuscular symptoms occurred in six instances following parenteral magnesium sulfate administration (table 1). This improvement became evident within six to 18 hours following the onset of therapy, and was dramatic in cases 2, 3 and 4. Improvement following re-institution of a normal diet occurred in cases 6, 7, 8 and 9. Administration of calcium, magnesium, and potassium was associated with cessation of the status epilepticus in case 5. Intravenous calcium administration, tried initially in in cases 2 and 3, failed to improve the clinical disorder and actually appeared to intensify the neuromuscular symptoms.

In case 10, clinical improvement was apparent *only* during significant

elevations of the serum magnesium (6 to 8 mEq./L.). A return to normal serum magnesium values was associated with the return of symptoms despite significant retention of the magnesium ion. The improvement in case 1 *might* have been related to the nonspecific pharmacologic effect of a high serum magnesium concentration.[77] Death (pulmonary embolus) prevented further studies.

Relationship of Clinical Response to the Serum Electrolytes: A lack of precise correlation between the depressions of the serum magnesium and clinical symptomatology was apparent by the subsequent course in cases 2, 4, 5 (tables 2, 3 and 4) and case 8. Low serum values occurred without symptoms. Similarly, the serum calcium and the magnesium-to-calcium ratio in the serum appeared to be unrelated to the presence of symptoms.

Relationship of Symptoms to Renal Failure: Case 1 demonstrated the most severe psychiatric and neuromuscular symptoms nine days following a period of transient oliguria and moderate nitrogen retention. Recurrence of urinary tract obstruction and anuria in case 11 was associated with a sudden worsening in his psychiatric and neuromuscular symptoms. Low serum magnesium concentrations were present in case 1, and normal values were recorded in case 11.

The Effect of Magnesium Administration on Calcium and Phosphorus Metabolism: When magnesium sulfate represented the *only* additional electrolyte therapy, three patients (cases 2, 4 and 6) showed an associated rise in the serum calcium and alkaline phosphatase, and two (cases 4 and 6) showed a rise in serum phosphorus. Magnesium sulfate therapy was accompanied by increased calcium excretion that was moderate in cases 2, 10 and 11 and marked in cases 4, 5 and 6. Phosphorus excretion remained essentially unchanged during this therapy.

Electromyograms: While patterns of asynchronous muscle twitchings and tremors occurred in both cases 4 and 10, the tremor pattern was significantly more pronounced in case 10, and twitchings characterized the disturbance in case 4. The muscle activity showed no relation to electroencephalographic activity, and photic stimulation produced no change in any of these tracings.

Electroencephalograms: Diffusely abnormal tracings were recorded in six patients (cases 2, 4, 5, 8, 9 and 10). Nonspecific slowing and low voltage characterized all initial tracings. Improvement in the electroencephalograms occurred following magnesium therapy within days in case 4, within weeks in case 9, and within weeks following both calcium and magnesium therapy in cases 2 and 5. The state of the electroencephalograms showed no correlation with the concentrations of the serum magnesium or calcium in cases 2 and 5, and the electroencephalographic improvement generally lagged behind the clinical improvement in all patients.

Electrocardiograms: Interpretation of tracings in seven patients (cases 2, 4, 5, 7, 10, 11 and 12) was complicated by the presence of other disease

states, and frequently by disorders in the metabolism of several electrolytes. A uniform observation, however, was generalized and nonspecific ST segment depressions and low T wave voltage. Improvement toward normal occurred following magnesium administration in cases 4 and 11, and following the administration of magnesium, calcium and an improved state of nutrition in cases 2, 5 and 7.

Cerebrospinal Fluid: The routine analysis (pressure, protein and serology) of the cerebrospinal fluid was normal in four patients (cases 2, 5, 8 and 9). The concentration of magnesium was unchanged from that on normal cerebrospinal fluid for this laboratory (2.0 mEq./L.), despite the low serum values in these symptomatic patients.

Pathology: As yet, no lesions have been observed that are comparable to those witnessed in magnesium-depleted animals.[5, 8, 61, 78-83] Examination of tissues obtained at autopsy in cases 1, 5, 7, 10, 11 and 12, and by surgical biopsy in cases 2 and 4, failed to show any consistent abnormality with conventional or special staining technics. Endocrine abnormalities (including parathyroid gland examination), bone changes or tissue calcifications were not observed, and renal lesions included only the pathologic changes pertinent to the known preëxisting renal disease (cases 5, 7 and 12).

Discussion

Studies in 11 patients have revealed data suggesting that total body depletion of magnesium may result in psychiatric and neuromuscular symptoms. Such a causative relationship between depletion of the total body magnesium and neuromuscular symptoms was first appreciated from studies in animals.[1-9, 53, 80] The discovery of low serum magnesium concentrations in farm livestock spontaneously developing "lactation tetany" or "grass staggers" [2-4, 7] has led to extensive investigation of this ion in animals. A neuromuscular syndrome, not unlike that witnessed in our human subjects, can be produced in animals by specifically depleting the organism of magnesium,[1, 4, 5, 8, 9, 53, 80, 84] and can be corrected or prevented by the administration of magnesium salts.[6, 8, 85]

There have been few studies of the role of disordered magnesium metabolism in man. Low serum magnesium concentrations have been reported in a variety of clinical conditions, frequently in association with mental and neuromuscular symptoms.[10, 15, 16, 18, 20-28, 30, 31] The latter have included muscle twitchings and tremors, cramps, choreiform and athetoid movements and, rarely, convulsions. While clinical improvement has followed the administration of magnesium, reported data have not been sufficient to document a state of magnesium depletion or, if present, to identify its etiology. It is hoped that the data in the present study will clarify some of these relationships.

No measure of total body magnesium was available in this study, either by direct tissue analysis [86, 87] or by radioactive technics,[88] and thus a state

of magnesium depletion must be inferred from the balance data. An individual in magnesium balance should retain virtually none of a parenteral dose of magnesium,[28, 55, 89] while human subjects specifically depleted of magnesium retain significant amounts of the administered ion.[89] The large retentions recorded in cases 1, 2, 4, 5, 10 and 11 were therefore believed to reflect large depletions of the total body magnesium in these individuals. The preëxisting renal impairment in cases 1 and 11 possibly contributed to the retention of magnesium, although the magnitude of this retention seemed much greater than might be expected for the degree of impairment in the filtration rate recorded during these collections. Data on the excretion of a parenteral magnesium load under these conditions are not readily available. The marked renal conservation of magnesium in the presence of adequate dietary intake reflected a markedly positive magnesium balance in several other patients, also suggesting a previous state of magnesium depletion.

It should be recognized, at this point, that the serum concentration of magnesium need not precisely reflect the state of the toal body magnesium. Since the extracellular phase of this ion represents such a small portion of the total body content,[45, 46] it is conceivable that a total body depletion might exist in the presence of normal serum levels, and, conversely, low serum levels need not imply a total body depletion of this ion. Evidence that the former condition might exist is seen in case 10 and elsewhere.[17, 26, 89–92] As yet, evidence has *not* been presented to show conclusively that low serum values might exist *without* total body depletion of magnesium, or immediately following the correction of such a state.

The etiology of the presumed depletion of total body magnesium in these patients is not entirely clear. In most instances the expected renal conservation of magnesium[89, 93–95] was effective in reducing the urinary losses of magnesium to a minimum in the presence of a markedly reduced dietary intake of magnesium. Fecal losses of magnesium are generally considered to consist mainly of the unabsorbed magnesium in the diet, plus small amounts contained in and poorly reabsorbed from the intestinal juices.[9, 11, 45, 55, 88] It is uncertain whether these latter sources of loss could have produced a significant depletion of magnesium in those patients with severe diarrhea. Studies in case 2 and in other reports[9, 89, 93] suggest that such losses might indeed deplete the body of magnesium.

Renal "wasting" of magnesium, of a transient nature, was observed in case 5. This phenomenon might have been related to the severe muscular activity of the epileptic seizures,[96, 97] or to the hypokalemic alkalosis which was subsequently corrected. Hypomagnesemia and excessive renal excretion of magnesium have been reported previously in two individuals with "primary aldosteronism" and potassium depletion.[98, 99] Following restoration of the total body potassium in these patients, these phenomena showed correction toward normal, and a positive magnesium balance ensued. In

a different type of study (dietary restriction of magnesium in normal man), the pronounced renal conservation of magnesium associated with a low magnesium diet was unaltered by simultaneous potassium depletion and alkalosis.[89] This situation, however, differs from those mentioned above and from case 5 in that the duration of the depletion was brief and hypokalemia was *not* observed. It is of interest that evidence of potassium depletion was present in several of the cases of "magnesium deficiency" previously reported.[16, 18, 26, 27] Unfortunately, excretion data in these cases were not presented.

Hastening of symptomatology in experimental magnesium deficiency in animals has been induced by large intakes of both calcium and potassium.[100–102] Also, decreases in the serum concentration of magnesium have been observed following glucose administration in human subjects[55] and following calcium administration.[24, 103] Some of the patients in this and other reports[16, 18, 24, 26, 27] had received dextrose-containing fluids with potassium salts, and sometimes calcium salts. These factors must be considered as possibly having some effect on the movement of the magnesium ion. A sudden shift into the cells or onto the bone lattice might possibly explain the low serum magnesium values[24, 55, 103] and somehow produce the neuromuscular disorder. Such a shift of magnesium into the intracellular compartment might account for the sudden renal conservation of magnesium observed following recovery from prolonged starvation,[104] and the renal conservation and fall in serum magnesium following recovery from diabetic acidosis.[90–92, 105] It would seem unlikely, however, that the prolonged depressions of the serum magnesium noted in several patients of this report could relate solely to such a hypothetic movement of magnesium.

The dramatic disappearance of neuromuscular and psychiatric symptoms following magnesium therapy in some of the patients in this and other reports[15, 16, 18, 21, 23, 26, 27, 30] suggests a causal relationship between the symptomatology and the presumed depletion of magnesium. It is possible, however, that the disordered metabolism of magnesium was an associated rather than a causal factor in these disorders, wherein the improvement following magnesium therapy might have resulted from some nonspecific action of magnesium on neuromuscular function. While such a possibility cannot be entirely ruled out, normal or low serum magnesium values obtained subsequently in several patients exclude from consideration a sedative action of the magnesium ion in this improvement.[77, 106]

Should a relative depletion of the magnesium ion be etiologic in these disorders, its site and mechanism of action are to be determined. Certainly the low serum magnesium concentration is *not* of primary significance, nor are the depressions of the serum calcium or the ratio of the serum magnesium to calcium of prime importance. Various data suggest that an intracellular deficit of magnesium, or a change in the intracellular-to-extracellular ratio, might be of primary significance: (1) the delay in clinical improvement

following magnesium administration noted in all subjects in this and other studies;[8, 18, 22, 26, 27] (2) decrease in the abnormal neuromuscular irritability in magnesium-deficient animals following *prolonged* magnesium therapy, but not *immediately* following an infusion of magnesium salts;[8, 85] (3) absence of symptoms despite low serum values of magnesium, as shown in cases 2, 5, 6 and 8 and elsewhere.[14, 17–19, 23, 27, 30, 107]

The frank failure of response in case 10 despite sizable doses and retention of magnesium suggests that the mental and neuromuscular symptoms of delirium tremens (at least as seen in this one patient) probably have their pathogenesis related to multiple factors rather than to magnesium depletion alone.

Combined analysis of the clinical observations, electromyographic and electroencephalographic data in these patients suggests that the disordered neurologic function was occurring in at least two locations: the brain, and at some lower level, such as the spinal cord, peripheral nerve or neuromuscular junction. Previously, the midbrain had been implicated in the pathophysiology of the neuromuscular disorder, at least in magnesium-deficient animals.[85] Magnesium has been shown to play an important role in neuromuscular irritability,[85, 108] in the contractile function of muscle[109] and in numerous enzyme systems.[85, 110, 111] Blaxter, reviewing the studies in animals, has suggested that the symptomatology in magnesium deficiency might well relate to disturbances in enzyme systems dealing with neuromuscular transmission.[112] Recent investigation has yielded evidence at least consistent with the hypothesis that depletion of magnesium at a site such as the motor end-plate might result in heightened neuromuscular activity, perhaps through increased acetylcholine production or release.[113–116] It is not clear what role potassium administration, or the retention of potassium and sulfate ions (renal disease), might play in increasing neuromuscular irritability, particularly in states of magnesium depletion. Factors such as cation binding and shifts in the tissue cations[117, 118] certainly must be considered in future studies.

Direct chemical analysis of tissues from magnesium-deficient animals has shown positive[97, 119, 120] and negative[8, 112] evidence for depletion of magnesium from the tissues of the nervous system. If such a tissue depletion does indeed exist in these disorders, improved technics for measuring the intracellular magnesium content[86, 87] must define and locate this depletion more precisely. A better understanding of the relationship of intracellular to extracellular magnesium is also essential, since it may well be that this is of prime importance in the physiology of neuromuscular function, in a manner akin to the role of potassium in muscle physiology.[117]

The depressions in serum calcium observed in all patients of this study are of considerable interest. Such depressions have on occasion been noted in both animals[2, 3, 7, 8, 84, 93] and man[17, 26, 27] presumably depleted of magnesium. The etiology is not clear. Decreased intestinal absorption of

calcium and an increased vitamin D requirement have been reported in magnesium-deficient calves.[84] Tissue analysis in animals has shown that, under conditions of experimental magnesium deficiency, magnesium depletion occurs primarily from bone, while a concurrent increase occurs in the bone calcium[8, 96, 97, 112, 119, 120, 121] and occasionally in the soft tissue calcium.[97, 119] Unfortunately, calcium balance data were not sufficiently complete in all of the patients of the present study to define more precisely the etiology of the hypocalcemia. A reasonable explanation (malabsorption) was available in only two instances (cases 2 and 6), and possibly in a third (case 12). Hypoproteinemia could not always explain the observed depressions, and excessive renal losses of calcium were not observed. It is of interest that in three instances the administration of magnesium sulfate alone was associated with prompt increases in the serum calcium. The increments in urinary calcium excretion following magnesium therapy occasionally seemed greater than might be expected,[51, 55, 122] but data pertaining to calcium excretion following magnesium administration in malnourished patients such as these are not available for comparison. While increases in calcium excretion have been observed following the administration of salts of magnesium other than the sulfate,[11, 51, 55, 123] this latter ion might have contributed somewhat to an increase in the cation excretion.[118]

It is of interest that Fitzgerald and Fourman noted greater calcium excretion following magnesium administration in the presence of experimental magnesium deficiency than occurred in their human subjects when they were not deprived of magnesium.[89] These data, the results of tissue analyses in animals,[8, 96, 97, 112, 119, 120, 121] and the data in our patients might suggest that in the presence of magnesium depletion, calcium (and perhaps phosphorus) is sequestered excessively onto the bone lattice or into soft tissues. In such a situation, magnesium "repletion" might permit release of this calcium from the tissues, thereby increasing the serum concentration and renal excretion of calcium. It is equally possible that the processes producing the depletion of magnesium in these malnourished individuals also caused a total body depletion of calcium and phosphorus. While either of these two mechanisms could conceivably produce the observed depressions in serum calcium and phosphorus and the decreased renal excretion of these substances, the relationships between these electrolytes remain unclear.

Summary and Conclusions

1. Observations in 12 patients suddenly developing psychiatric and neuromuscular symptoms have revealed evidence suggesting a relationship between these symptoms and a depletion of the total body magnesium.

2. Nine patients demonstrated significant depressions of the serum magnesium concentrations, and all demonstrated low serum calcium values.

3. Administration of magnesium by the parenteral route or in the diet was associated with clinical improvement. This, on occasion, was dramatic.

In several instances, abnormal electroencephalograms and electrocardiograms improved following therapy. Calcium administration *alone* failed to correct the neuromuscular disorder in two of these patients, and may actually have intensified the symptoms.

4. Magnesium administration usually resulted in a markedly positive magnesium balance, on occasion associated with significant increases in the serum calcium concentration and in the renal excretion of calcium.

5. Underlying clinical features, probably concerned in the etiology of the presumed magnesium depletion, were severe malnutrition and usually some source of fluid and electrolyte loss, such as vomiting or diarrhea. Excessive renal excretion of magnesium, observed in one patient, is thought to have been related to a state of potassium depletion.

6. While it is not clear how magnesium depletion produces symptoms, considerable evidence suggests that an intracellular depletion of this ion is of primary significance.

7. Increased awareness of the clinical importance of magnesium and improved technics for studying the distribution and function of this ion will undoubtedly clarify the precise role of the magnesium ion in disease states. At the present time, however, it is clinically important to recognize the possibility of magnesium deficiency as a causative factor in disturbances of neuromuscular and central nervous system activity, particularly in patients with malnutrition due to any cause.

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Summario in Interlingua

1. Observationes in 12 patientes, qui subitemente disveloppava delirio e disordines neuromuscular characterisate principalmente per extense tics muscular, ha revelate datos que suggere un relation inter iste symptomas e un depletion del magnesium del corpore total.

2. Nove del 12 patientes monstrava significative depressiones del concentration de magnesium in le sero. Omnes habeva basse valores pro calcium seral.

3. Le administration de magnesium per via parenteral o dietari esseva associate con melioration clinic. In certe casos, le grado del melioration esseva dramatic. In plure casos, anormalitates electroencephalographic e electrocardiographic se meliorava post le therapia. Le administration de calcium sol non corrigeva le disordine neuromuscular in duo patientes del serie. Possibilemente illo mesmo intensificava le symptomas in iste casos.

4. Usualmente le administration de magnesium resultava in un marcatemente positive balancia de magnesium. In certe casos isto esseva associate con un augmento significative in le concentration de calcium del sero e in le excretion renal de calcium.

5. Le subjacente aspectos clinic, que esseva probabilemente implicate in le etiologia del presumite depletion de magnesium, includeva sever grados de malnutrition e usualmente le un o le altere causa de perdita de fluido e electrolytos, per

exemplo vomito o diarrhea. Excessos del excretion renal de magnesium, observate in un del patientes, es interpretate como relationate a un stato de depletion de kalium.

6. Ben que il non es clar per qual mechanismo le depletion de magnesium produce su symptomas, il existe varie observationes que suggere que un depletion intracellular de iste ion possede un signification primari.

7. Augmentate attention prestate al importantia clinic de magnesium e meliorate technicas pro le studio del distribution e del function de iste ion va sin dubita clarificar le rolo precise del ion de magnesium in statos pathologic. Tamen, al tempore presente il es importante ab le puncto de vista clinic que on recognosce le possibilitate que un carentia de magnesium es un factor causative in disturbationes del activitate neuromuscular e del activitate del systema nervose central, specialmente in patientes con malnutrition per non importa qual causa.

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THE DYSGAMMAGLOBULINEMIC SYNDROME*†

By William J. Hammack, M.D., F. Elna Bolding, B.S., and Walter B. Frommeyer, Jr., M.D., F.A.C.P., *Birmingham, Alabama*

Plasma protein electrophoretic patterns revealing discrete and homogeneous globulin peaks have been interpreted to indicate either multiple myeloma, cryoglobulinemia or macroglobulinemia. The increased serum globulin found in cirrhosis, hyperglobulinemic purpura and hepatitis exhibits on paper electrophoresis diffuse and rounded peaks that are distinct from the discrete and homogeneous serum electrophoretic peaks found in the patients forming the basis of this report. Four male patients with discrete serum gamma globulin electrophoretic peaks have been observed for from two to three and one-half years without evidence of specific disease other than an inordinate susceptibility to infections. Although multiple myeloma may subsequently develop in these patients, it is believed that the symptom and laboratory complex observed in these patients should tentatively be considered as a separate syndrome from those previously described.

Materials and Methods

All blood samples were drawn in the fasting state.

Serum Electrophoresis: Paper electrophoresis was performed using the Spinco Model R system.[1]

Urine Electrophoresis: Paper electrophoresis was performed on aliquots of 24-hour urine specimens. Thirty milliliters of urine were concentrated by dialysis against 20% polyvinyl pyrrolidine for from 24 to 48 hours. Exactly 0.05 ml. of the concentrated dialysed urine was applied to the filter paper strip for electrophoresis and was treated in the same manner as the serum specimen.

Bence Jones Protein Test: The method of Jacobson and Milner was used.[2]

Ultracentrifuge Analyses of Serum: A Spinco Model E analytic ultracentrifuge was used. The serum to be analyzed was diluted by adding two volumes of 0.2 molar sodium chloride solution to one volume of serum. The maximal speed of the ultracentrifuge was 59,780 rpm, and photographs were made at eight-minute intervals after the maximal speed was obtained. To determine the amount of macroglobulin with a sedimentation constant

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From the Department of Medicine, University of Alabama College of Medicine, and Veterans Administration Hospital, Birmingham, Alabama.

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Requests for reprints should be addressed to Walter B. Frommeyer, Jr., M.D., Professor and Chairman, Department of Medicine, Medical College of Alabama, Birmingham, Alabama.

of S19 present in the serum of case 4, planimeter tracings were made using a Spinco Model RB analytrol. These values were used to calculate the per cent of the total protein represented by each of the peaks obtained by ultracentrifugation.

Total Serum Protein: The method of Wolfson et al.[3] was employed.

Serum Immunology: These studies were performed by Dr. Leonhard Korngold,* using a modification of the gel diffusion technic of Ouchterlony.[4, 5, 6] Normal human gamma globulin antiserum was placed in the central reservoir. In the surrounding four reservoirs were placed a Group I myeloma protein, normal serum, normal gamma$_2$ globulin and the unknown. The unknown was considered to be a "myeloma" protein if characteristic spurs were formed between the precipitin lines during gel diffusion.

Properdin Assays: A modification of the method of Pillemer et al.[7] was used.† By this method the average normal value is four units per milliliter. The lower limit of normal is considered to be 1.5 units per milliliter.

Case Reports

Case 1 (figure 1). This 64 year old Negro male truck driver was admitted to the hospital for the first time in November, 1954, with a chill, fever and the sudden onset of lumbar pain as his only symptoms. On admission, physical examination was within normal limits, even though laboratory studies revealed a leukocytosis with a slight shift to the left, and pneumococci were cultured from the blood on two occasions. During this admission he developed an acute arthritis of his right knee, the fluid from which was purulent but sterile. The total serum protein was 8.4 gm.%, the globulin comprising 4.2 gm.%. Four months later the patient again had pneumococcal septicemia, with a prompt response to antibiotic therapy. Approximately one year following this admission he was seen with fever, meningitis and a pneumococcal septicemia. At that time the total serum protein was 9.4 gm.%; albumin, 4.8 gm.%; globulin, 4.6 gm.%. There was an adequate response to antibiotics, even though the patient's condition was considered to be critical on admission. Sixteen months following this episode he developed a pneumococcal pneumonia which responded to antibiotics. Another episode of pneumonia and septicemia occurred in January, 1958, during which he also had hematemesis. This illness responded slowly to antibiotics, 13 ml. of gamma globulin over a five-day period, transfusions of whole blood and an ulcer regimen. Studies done over this three and one-half year period of time have revealed normal bone marrow on repeated aspirations, normal x-ray studies of the bones, and no Bence Jones proteins in the urine. No cryoglobulins have been found, and serum ultracentrifuge analysis has revealed no increase in macroglobulins (figure 8, No. I). The serum electrophoretic pattern has consistently revealed two gamma peaks. A protein with a mobility identical to one of the serum peaks was present in the urine in small amounts (figure 2). By immunologic gel diffusion technics the serum protein is antigenically Group I myeloma protein. Isohemagglutinin titer to anti-B was 1:10 (normal, 1:80 or higher), and the antibody response to a typhoid booster was grossly inadequate. Anticomplementary activity was repeatedly demonstrated. Properdin assay revealed 1.0 unit per milliliter. The serum on some occasions would coagulate irreversibly on heating to 56°C.

* Section of Immunology, Sloan-Kettering Institute for Cancer Research, New York, N. Y.

† These studies were performed by Dr. James A. Tullis, Blood Characterization and Preservation Laboratory of the Protein Foundation Incorporated, Boston, Massachusetts.

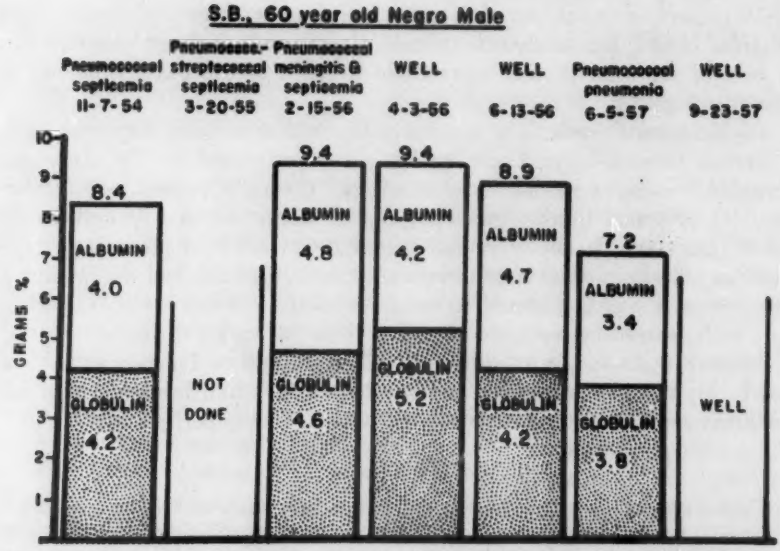

FIG. 1. Hospital course of case 1, compared with the levels of albumin and globulin. One additional episode of pneumonia has occurred.

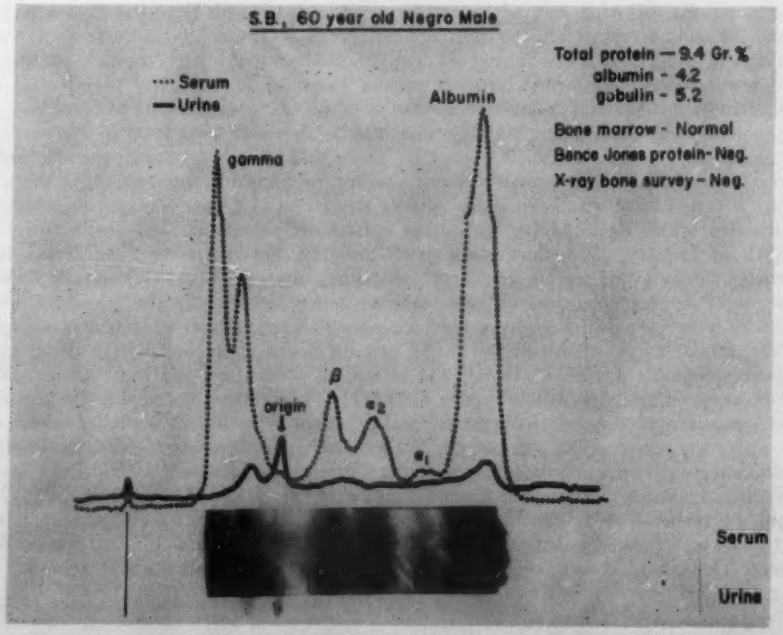

FIG. 2. Serum and urine paper electrophoretic patterns of case 1. The serum pattern shows two sharp gamma peaks, and the urine pattern shows a gamma peak as well as a small amount of albumin.

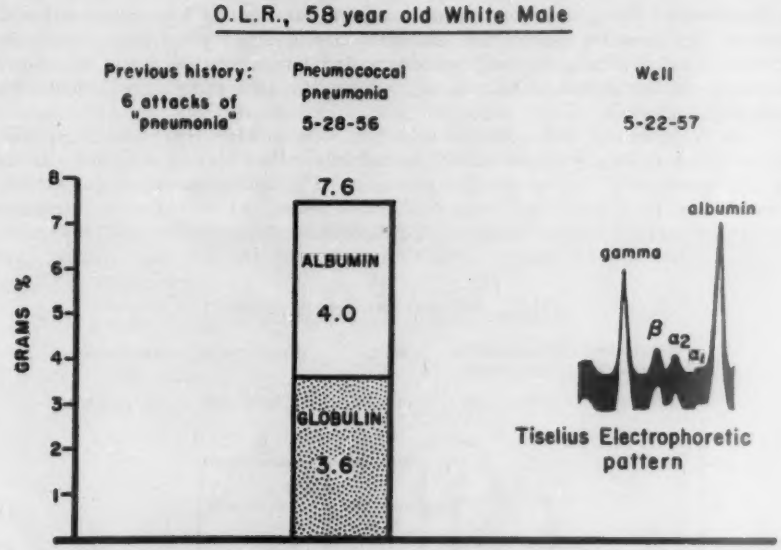

FIG. 3. See text for explanation. The Tiselius electrophoretic pattern on the serum shows a definite increase composed of a sharp gamma globulin peak.

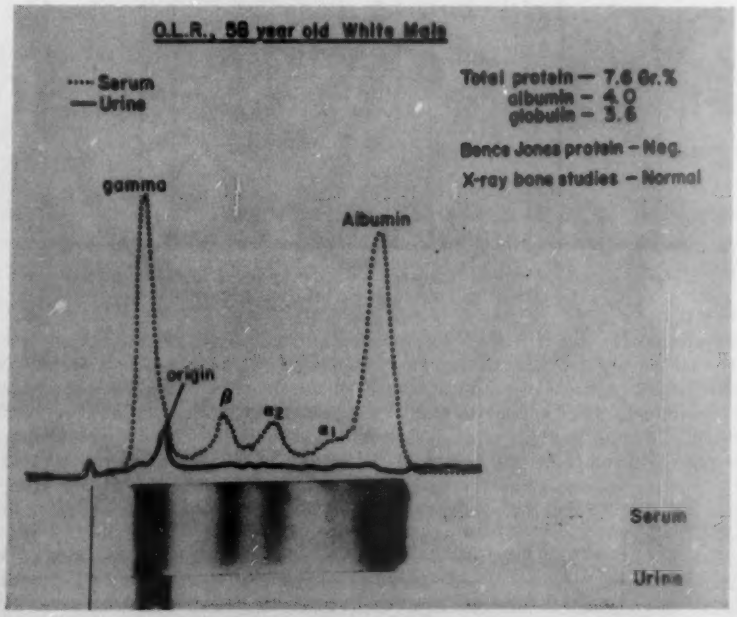

FIG. 4. Serum and urine paper electrophoretic patterns of case 2. A sharp gamma peak is present in the serum, and gamma globulin is present in the urine.

for 30 minutes. Pyroglobulins in previous reports have usually been associated with myeloma. In summary, during the last three and one-half years this patient has had five episodes of pneumococcal septicemia, and serum electrophoresis has shown the presence of two gamma peaks without other evidence of myeloma, cryoglobulinemia or macroglobulinemia.

Case 2 (figure 3). This 58 year old white male was hospitalized in May, 1956, because of an episode of pneumococcal pneumonia. Past history disclosed that he had had "pneumonia" on six previous occasions. Physical examination was entirely normal except for a few palpable inguinal lymph nodes and mild obesity. Response to penicillin therapy was satisfactory. Total serum protein was 7.6 gm.%; albumin, 4.0 gm.%; globulin, 3.6 gm.%. Properdin assay was 0.7 unit per milliliter, and

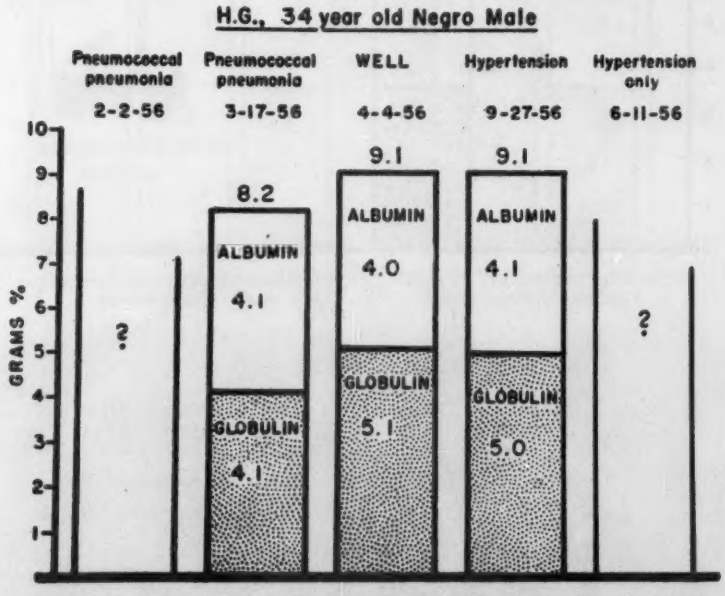

FIG. 5. Hospital course of case 3, compared with the levels of albumin and globulin. One additional episode of pneumonia has occurred.

anticomplementary activity was demonstrated. The serum electrophoretic pattern revealed a sharply defined, tall gamma peak which has been constant on numerous determinations (figure 4). Electrophoresis of the urine revealed a small amount of protein with a mobility similar to that of the serum peak. Studies for cryoglobulins, macroglobulins and pyroglobulins have been negative. Bone marrow aspiration has been deferred throughout this two-year observation period in order not to alarm the patient. Periodic bone x-ray surveys, however, have not revealed evidence of myelomatous lesions. The ultracentrifuge pattern was normal and is shown in figure 8, No. II.

Case 3 (figure 5). This 34 year old Negro male had three episodes of lobar pneumonia over a seven-month period of time, the first episode in February, 1956. Response to antibiotics was excellent each time. Physical examination has been normal except for a blood pressure of 190/100 mm. of Hg. Repeated serum electrophoretic patterns have revealed a discrete gamma globulin peak which was slower

than normal gamma globulin (figure 6). Throughout a two-year period of time, repeated x-ray examinations have failed to reveal bone lesions. Bone marrow smears have been normal. The urine does not contain Bence Jones proteins, and the serum does not exhibit macroglobulins on ultracentrifuge analysis (figure 8, No. III). The total protein has risen to 9.1 gm.%, with 4.1 gm.% albumin and 5.0 gm.% of globulin. Immunologic gel diffusion studies revealed a protein similar to Group I myeloma proteins. Isohemagglutinin titer to Anti-A was 1:10 and to Anti-B was 1:5. This low titer has been observed repeatedly. Anticomplementary activity was present. No properdin assay was done.

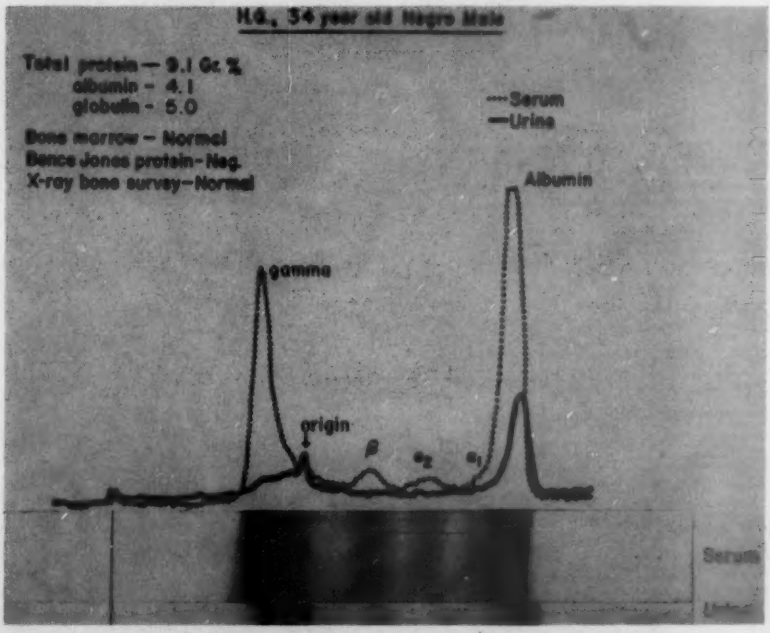

FIG. 6. Serum and urine paper electrophoretic patterns of case 3. A sharp gamma peak is shown in the serum, while both albumin and gamma globulin are present in the urine.

Case 4. This 39 year old white male was first seen in April, 1950, because of vague, recurrent upper left chest pain, the mechanism for which has not been clarified. Physical examination was within normal limits. Two weeks later he sustained an acute loss of vision of his left eye due to neuroretinitis. This disorder responded to cortisone, Artane and intravenous procaine. An unabsorbed heterophil agglutination titer was 1:224 at this time, and 1:128 one month later. One year after this episode the patient sought medical attention because of severe sudden left flank pain. After thorough study this pain was considered to be of muscular origin. Nine months later he developed some blurring of his vision, and stated that objects appeared to have a halo about them. Physical examinations and laboratory studies other than his abnormal electrophoretic pattern have been normal until this time. Subsequently, he developed unequal vision for which no etiology could be found. A routine history and physical examination two years later was within normal limits. Serum electrophoretic patterns during this two-year period have revealed on each occasion a sharp

peak located in the center of what appears to be normal gamma globulin (figure 7). Study of aspirated sternal bone marrow showed an increase in eosinophilic cells but no increase in plasma cells. The urine contained a small amount of protein having the same mobility as the sharp serum protein peak. Repeated studies on the serum for cryoglobulins have been negative, and ultracentrifugal analysis for macroglobulins revealed that the 19S component comprised 4.3% of the total protein (figure 8, No. IV). Immunologic gel diffusion studies revealed no abnormal proteins except a positive reaction with the antimacroglobulin antiserum. The homogeneous protein on electrophoresis comprised 16% of the total protein, and presumably would there-

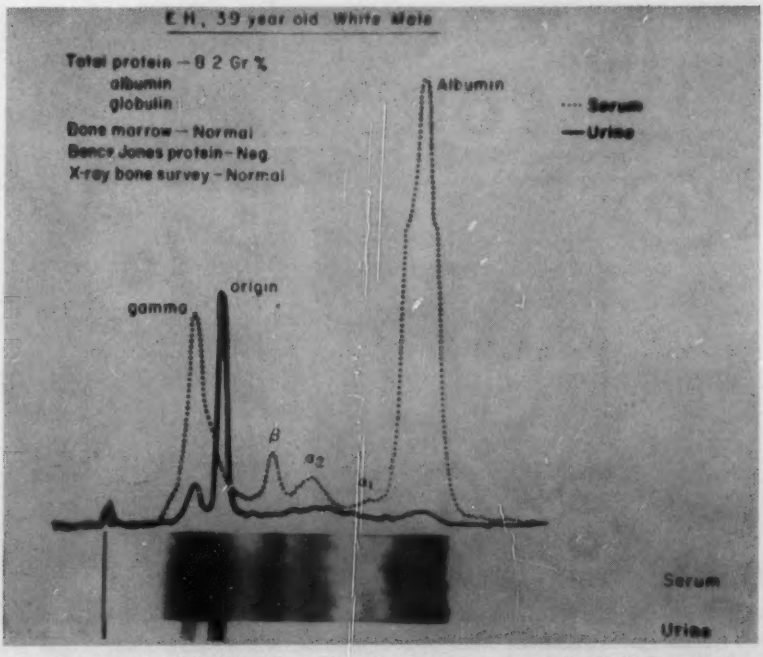

FIG. 7. Serum and urine paper electrophoretic patterns on case 4. A sharp gamma peak is present in the center of what appears to be normal gamma globulin.

fore not be made up entirely of macroglobulin. The properdin level of his serum was 1.5 units per milliliter. Isohemagglutinin titer to Anti-A was 1:125 and to Anti-B was 1:150 (normal, 1:80 or higher). Anticomplementary activity was present on one occasion but absent when a sterile specimen was obtained.

DISCUSSION

In recent years many disorders of protein synthesis have been described. These reports have been concerned primarily with deficient production of the plasma proteins, and include agammaglobulinemia,[8] afibrinogenemia,[9] a-betaglobulinemia [10] and an-albuminemia [11] (i.e., total absence of albumin). These disorders are usually congenital defects of protein synthesis, but oc-

casionally they may be secondary to other disease processes. Only in myeloma, however, has excessive and abnormal production of plasma proteins been described as a variety of electrophoretic mobilities having the characteristic of being sharply defined homogeneous protein peaks.[12]

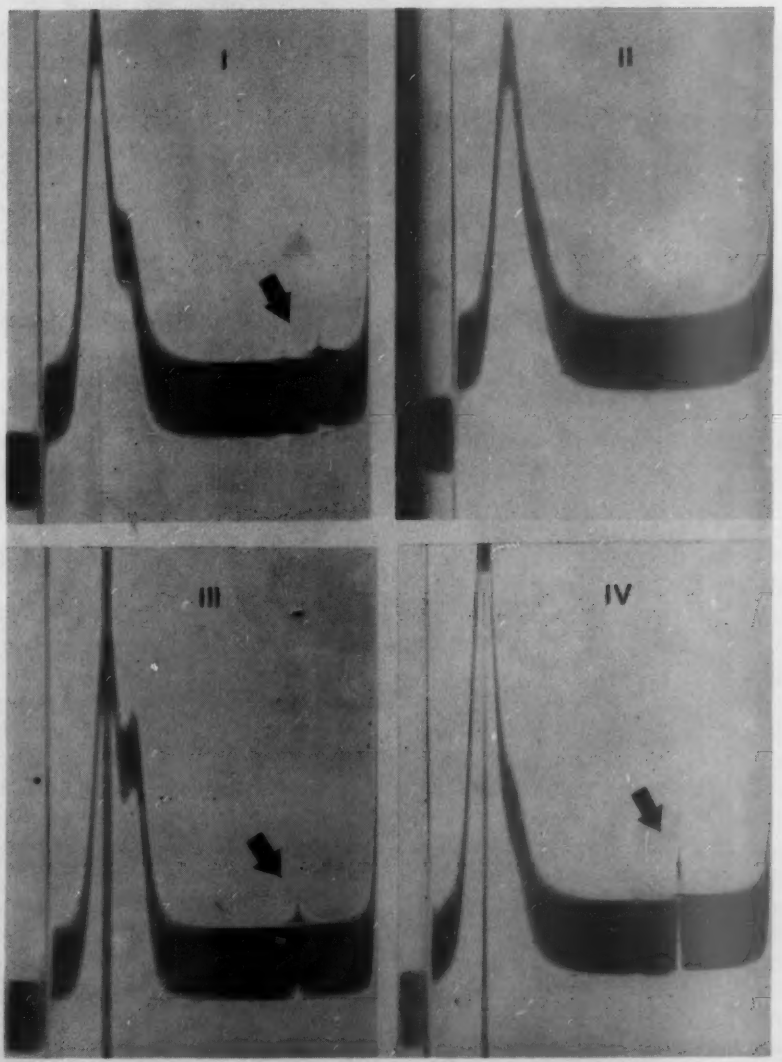

FIG. 8. Representative photographs of the ultracentrifuge analyses. Number I is case 1 and shows only a normal 19S component. Number II is case 2, with no demonstrable 19S peak. Number III is case 3, with a normal 19S peak. Number IV is case 4, with 4.3% (3.52 mg./ml.) of 19S globulin.

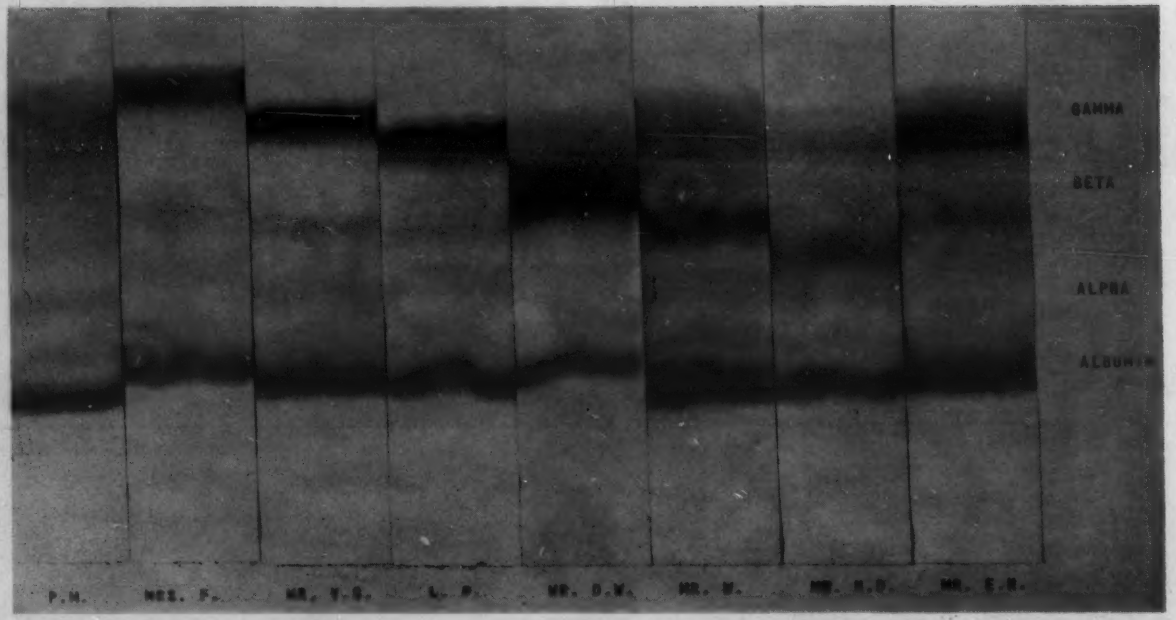

FIG. 9. · Paper electrophoretic patterns of serum from patients with dysproteinemias. From left to right: P. M., localized myeloma of spine with diffuse hypergammaglobulinemia. Mrs. F., "slow" gamma myeloma. Mrs. V. S., gamma myeloma. L. P., "M" myeloma. Mr. D. W., "slow" beta myeloma. Mr. W., beta myeloma. Mr. H. D., "slow" alpha myeloma. Mr. E. H., case 4 of this report.

Figure 9 illustrates various serum electrophoretic patterns of patients with myeloma that have been observed here during the last four years. Although the mobilities vary from that of slow gamma globulin to alpha globulin, the characteristic, sharply defined protein peaks are evident.

Abnormalities of protein synthesis producing unusual physicochemical properties, such as macroglobulinemia, have also been reported.[13] In this disorder the primary characteristic is a protein of high molecular weight. Cryoglobulins [13, 14] and cryofibrinogen,[15] usually associated with myeloma or various malignancies, have also been reported. Pyroglobulins [16, 17] (serum proteins which coagulate at 56°C.) have been found rarely in both serum and urine, and have usually been associated with myeloma. Since paper electrophoresis has made protein separation more easily possible on a large scale, another group of "dysproteinemias" appears to be emerging. The patients forming the basis of this report fall into such a group, although positive proof that these patients will not develop classic myeloma is still lacking. The observation by Bloom et al.[18] that anticomplementary activity in the serum may precede clinical myeloma by as long as 17 years stimulated a similar study in these patients. The serums of three of the four patients were found to have anticomplementary activity. Whether this observation has any prognostic significance will await long-term follow-up, but careful studies for as long as three and one-half years have failed to reveal evidence of myeloma in these patients.

The clinical picture in three of these four patients is that of repeated pneumococcal infection. On serum electrophoresis, one or more discrete homogeneous peaks have been found which formerly were considered to be characteristic of myeloma. Studies for macroglobulinemia by the ultracentrifuge method and by immunologic tests with rabbit antimacroglobulin antisera has been negative in all but case 4. The serum ultracentrifuge pattern in this patient revealed 4.3% macroglobulin, but this did not comprise the entire amount found on electrophoretic analysis. However, studies by Dr. Korngold, utilizing antimacroglobulin rabbit antisera have revealed what he believes to be evidence of an increased amount of macroglobulin. Since any amount of macroglobulin above 2 to 3% of the total protein is considered to be above normal, this represents a small but definite increase in 19S globulin. Because the antimacroglobulin antiserum reacts only with gamma macroglobulin, another possible explanation of this disparity is that there is a concomitant decrease in the normal alpha$_2$ macroglobulin with an increase in the gamma macroglobulin. Immunologic studies performed on the other patients in this series have demonstrated reactions with antisera that are typical for myeloma proteins. There appears, therefore, to be some similarity antigenically between the proteins found in the serums of these patients and the proteins present in myeloma. However, bone surveys have not shown evidence of myelomatous lesions, and repeated bone marrow studies have not revealed evidence of an increase in plasma cells in the pa-

tients reported herein. Smith has studied 13 patients with discrete gamma globulin peaks and has applied the term "non-myelomatous paraproteinemia" to this disorder.[19] Some of his patients had macroglobulins and some had cold-precipitable globulins (cryoglobulins). He noted an unusual incidence of chronic pulmonary disease. Owen and Rider [12] have reported four patients with discrete serum gamma globulin peaks but without other evidence of myeloma. Two of these patients had repeated episodes of pneumonia.

At present, since the authors believe that there is no justification for considering these patients to have classic myeloma, an unrelated name such as the "dysgammaglobulinemic syndrome" seems preferable. This term implies that in the patients in this present study there is a disturbed function of the gamma globulins which is manifested by repeated infections, and also that there may be multiple etiologies for this disturbed function.

Despite the elevated gamma globulins, three of these patients are clinically similar to patients with agammaglobulinemia, as demonstrated by a very low isohemagglutinin titer and a poor antibody response to typhoid vaccine injections. A similar situation may frequently be present in typical myeloma. Although only one of these patients has been treated with commercial gamma globulin, studies now in progress may determine if such gamma globulin will protect against repeated infections. The serums from three of the patients showed a low properdin level during an infection-free period. This may be an important factor in the unusual susceptibility of these patients to infection. The relationship between low serum properdin levels and the "dysgammaglobulinemia" remains obscure.

Summary and Conclusions

Four patients with unusual susceptibility to infection and an associated abnormal serum gamma globulin peak of a discrete homogeneous nature are reported. Immunologically the serum proteins of three of the patients were related to myeloma proteins, and in one of the patients the serum protein was related to macroglobulin. However, within the limits of a three and one-half year observation period, the authors consider that the protein abnormality in these patients, who have shown no evidence of classic myeloma, represents a new syndrome. Treatment has consisted of careful follow-ups and the use of antibiotics as soon as definite evidence of infection occurs.

Summario in Interlingua

Es presentate studios clinic e laboratorial effectuate in le casos de quatro patientes mascule. Tres habeva frequente pneumonias. In omnes, discrete piccos de globulina gamma esseva constatate in le electrophorese del sero. Studios ultracentrifugal non revelava macroglobulinemia, e tests pro cryoglobulinas e pyroglobulinas esseva negative. Studios immunologic per medio de technicas a diffusion de gel revelava que iste proteinas esseva simile a proteinas de "myeloma" in tres del patientes e a macroglobulinas in le quarte. Nulle indication clinic de myeloma o de anormalitates del medulla ossee esseva presente in ulle del patientes durante periodos de inter un e

tres e medie annos de observation. Le nivellos de properdina obtenite durante un periodo sin infection esseva basse. Le responsa immunologic a stimulation antigenic esseva pauco bon. Ben que hyperglobulinemia esseva presente, le syndrome clinic de hypoglobulinemia occurreva. Le tractamento ha essite un continue observation con le administration de antibioticos quando indicate. Studios currentemente in progresso va monstrar si injectiones de globulina gamma provide un protection contra iste repetite infectiones.

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TRENDS IN CANCER DEATH RATES AND CURE RATES*

By E. Cuyler Hammond, Sc.D., *New York, N. Y.*

The study of trends in the occurrence and management of a disease is important from three points of view: (1) it may give leads for further research on etiology, (2) it gives an indication as to whether we are on the right track in our efforts to control the disease, and (3) it gives some idea of what we may expect in the future, particularly in respect to needs for medical care and facilities. A few highlights of trends in cancer are presented, with emphasis on medical implications rather than etiology.

Trends in Death Rates

The death rate from a disease is dependent upon three major factors: (1) the age specific incidence rates, (2) the age distribution of the population, and (3) the cure rate, which may or may not be related to the age distribution of the patients.

As shown in figure 1, the crude cancer death rate—that is, the number of cancer deaths in a year divided by the total population—has been increasing steadily in the United States, England and Wales, Switzerland and the Netherlands. The same thing has happened in most countries for which we have adequate data. However, this increase is due in large measure to the fact that the population of these countries has become older, on the average, as a result of the improvement in life expectancy, coupled with changes in birth rates.

Figure 2 shows age-standardized cancer death rates for white males and females in the United States from 1930 through 1956. It is seen that when the aging factor is taken into account, the cancer death rates for females have been steadily declining for a number of years. However, the male rate has been increasing. A large part, though not all, of the increase in the rate for males is due to the phenomenal rise in the lung cancer death rate for this sex.

The comparable figures for England and Wales are shown in figure 3. The age-standardized cancer death rate for females has been declining, as in the United States. For males the total cancer death rate is increasing, but only because of the rise in lung cancer death rates. Except for lung cancer, the rate for males has been declining quite steadily since 1936.

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Requests for reprints should be addressed to E. Cuyler Hammond, Sc.D., Director, Statistical Research Section, American Cancer Society, 521 West Fifty-seventh Street, New York 19, N. Y.

In Switzerland, with a relatively small population, the cancer death rates fluctuate considerably from year to year (figure 4). The age-standardized cancer death rate for females shows some decline since 1938. Except for lung cancer, the rate for males shows a more marked decline than does the rate for females.

Figure 5 shows trends in age-standardized death rates from cancer of several important sites in the white male population of the United States from 1930 through 1956.

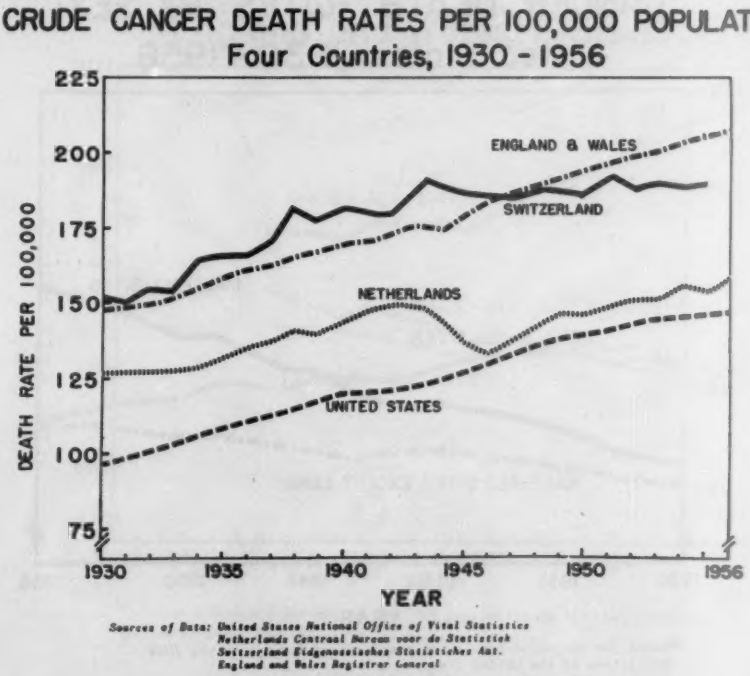

FIG. 1.

A decline in age-standardized death rates means either that cure rates have improved or that the incidence of the disease has decreased, or both. A rise in age-specific death rates ordinarily means that the incidence rate of the disease has increased, although it could mean that the cure rate has become poorer. This, of course, assumes that the data are reliable. However, it must be borne in mind that changes in reported death rates from specific diseases can result from improvement (or at least changes) in diagnosis over the years. Let us consider the figures with these facts in mind.

Among males, the death rates from lung cancer have increased dramatically. This cannot be attributed to a worsening of cure rates, since

the cure rate for lung cancer is and always has been very low. It is probable that a part of the rise is due to improvements in diagnosis, but this explanation applies with greatest force to an earlier period than is shown in figure 5. The great majority of experts who have studied the problem carefully are now in agreement that most of the rise in lung cancer death rates, particularly in recent years, is due to a corresponding increase in incidence rates. It is beyond the scope of this paper to discuss the reasons for this increase.

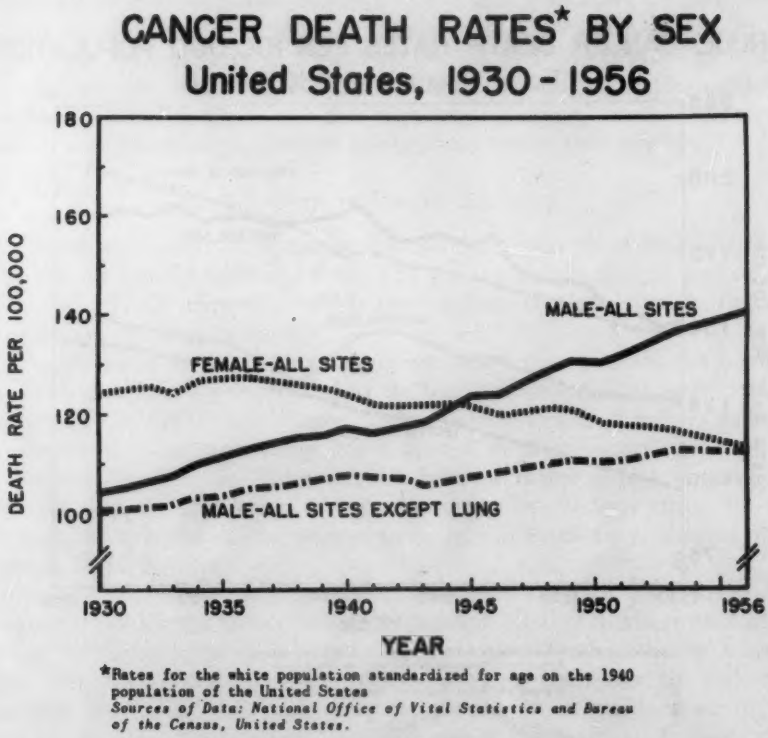

FIG. 2.

However, regardless of the cause, the increase in lung cancer is a matter of great concern in this period of medical history when death rates from the majority of diseases are declining and very few indeed are increasing.

Death rates from cancer of the stomach have been declining rapidly, a finding which cannot be attributed to improvements in cure rates, since the over-all cure rate for this disease is still very small. Data from the Cancer Registry of New York State give strong support to the conclusion that the incidence rate of stomach cancer has declined commensurate with the decline in the death rate.[1] This is one of the most puzzling things in the whole

cancer picture, and no satisfactory explanation has yet been found. Some people are of the opinion that the apparent rise in the rate for cancer of the pancreas is due to better diagnosis, proposing that in earlier years cancer of the pancreas was often confused with cancer of the stomach. Even if this is true, it would have little effect on the rates for stomach cancer, which are at a very much higher level than are the rates for pancreas cancer.

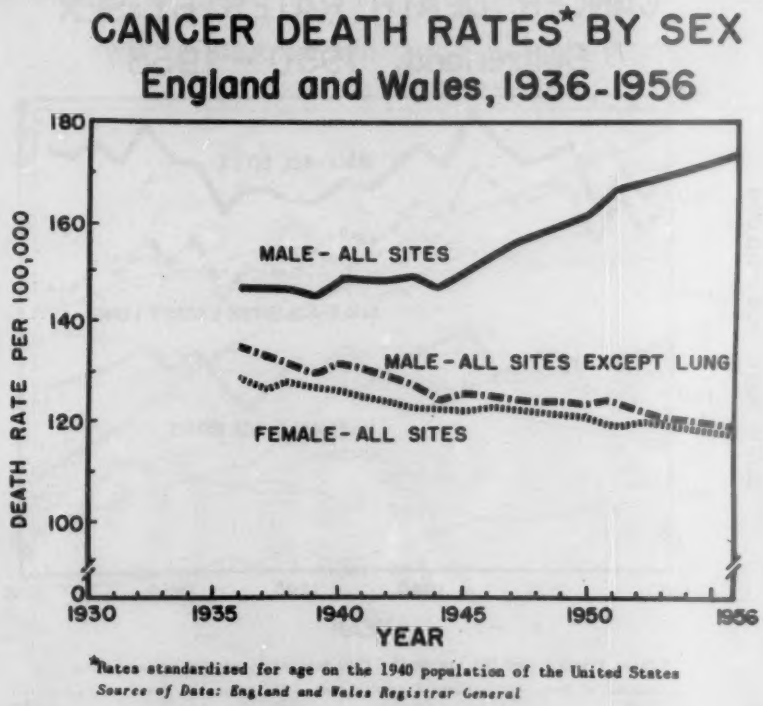

FIG. 3.

The rates for skin cancer have shown a steady decline, and the rates for cancer of the rectum have declined in the last few years. Data from other sources suggest that this may be due, in part at least, to improvements in cure rates.

Figure 6 shows trends in age-standardized death rates for cancer of several sites in the white female population of the United States. The rates for cancer of the uterus have declined steadily, and there is reason to suppose that this is due partly, or perhaps wholly, to improvements in cure rates. On the other hand, the rate for cancer of the breast shows almost no change from 1930 through 1956. This is a disappointment, considering the intensive effort which has been made in recent years to control this

disease. Conceivably, the present effort will show up in lower death rates from breast cancer during the next decade, but this remains to be seen. Lombard [2] has suggested that there actually has been a decline in breast cancer death rates, but that this has been obscured by improvement in diagnosis of primary site.

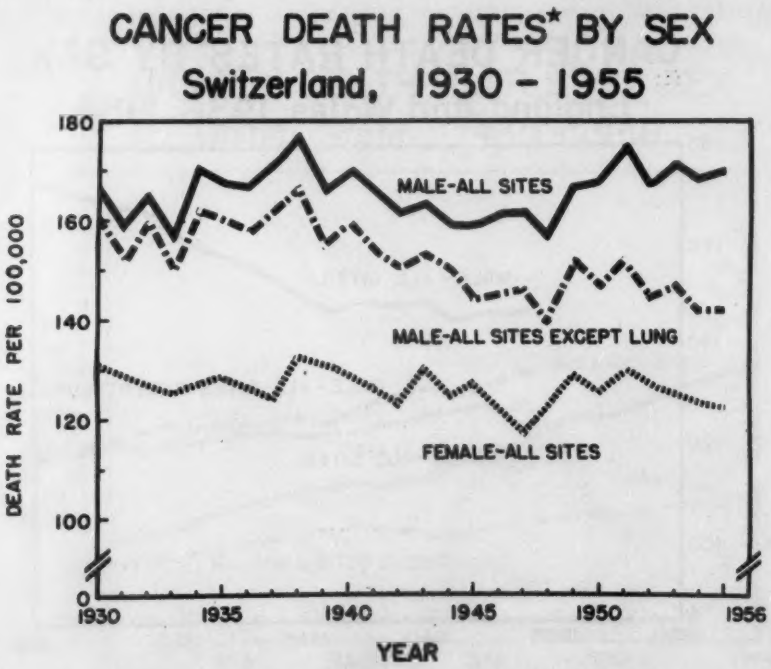

FIG. 4.

Lung cancer death rates have increased in females but not so rapidly as in males. The rise in the death rate from cancer of the ovary is one of our many puzzles.

Age-standardized death rates for cancer of several important sites are shown in figure 7 for the male population of England and Wales from 1936 through 1956. The picture is much the same as for the white male population of the United States, except that the rate for cancer of the stomach shows a somewhat less rapid decline and the rate for cancer of the rectum shows a more marked decline.

The picture for females in England and Wales is, in general, similar to the picture for white females in the United States (figure 8). However,

there are some differences in absolute levels and slopes of the trend lines for cancer of specific sites.

Trends in Survival Rates

Although countless papers have been published on cure rates for cancer of various sites, most of these cover only the experience of one hospital or one doctor. Surprisingly few data are available on long-term trends in

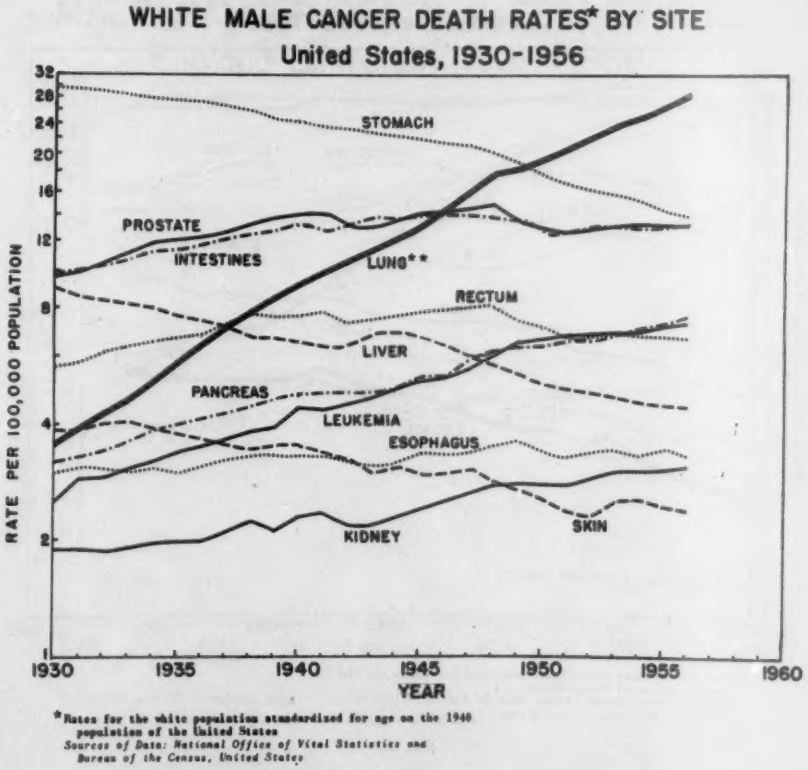

Fig. 5.

cancer cure rates for entire population groups (such as a whole nation or an entire state). One of the best sources of information on the subject is the Connecticut Cancer Registry, which has covered virtually the entire population of that State since 1935.

The Connecticut experience is one of the most heartening pieces of news in the entire cancer picture. Table 1 shows the five-year survival percentages for cancer of all sites for males and females initially diagnosed in three periods of time: 1935–1940, 1941–1946 and 1947–1951. For males, the

five-year survival rate increased from only 19% for the period 1935–1940 to 25% for the period 1947–1951. For females, the survival rate increased from 29% to 38% during the same interval of time.

Based upon these figures, supplemented by data from other sources, it is estimated that approximately one third of all cancer patients currently being treated in the United States will pass the five-year survival mark.[3]

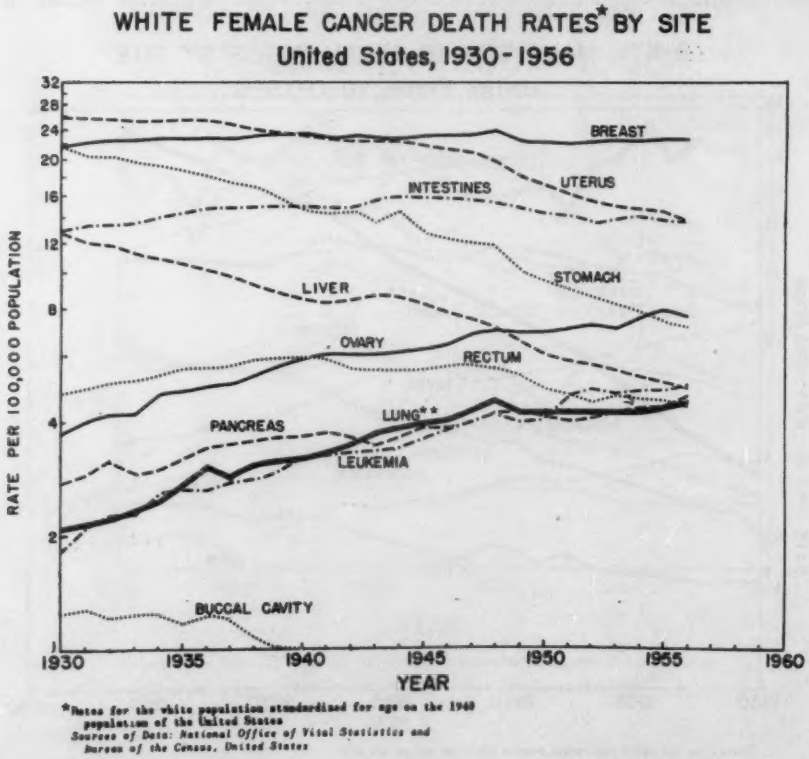

FIG. 6.

This is a marked improvement, since it is estimated that only a decade or two ago just about one quarter of those who got cancer survived for five years.

Most of the improvement just noted occurred because of increased survival rates for cancer of sites shown in table 2. Cancer of the colon and cancer of the rectum both showed splendid improvement, the five-year survival rate being over twice as high for the period 1947–1951 as for the period 1935–1940. Cancer of the prostate showed almost as much improvement as did cancer of the colon and rectum, and cancer of the corpus uteri

as well as of the cervix uteri showed a substantial improvement in survival rates. Cancer of the breast, bladder and stomach improved somewhat in survival rates.

It will be noted that for cancer of these sites the five-year survival rate improved for cases with regional involvement as well as for cases where the disease was localized at the time of diagnosis. This is a strong indication that the improvement was due primarily to more effective treatment, the

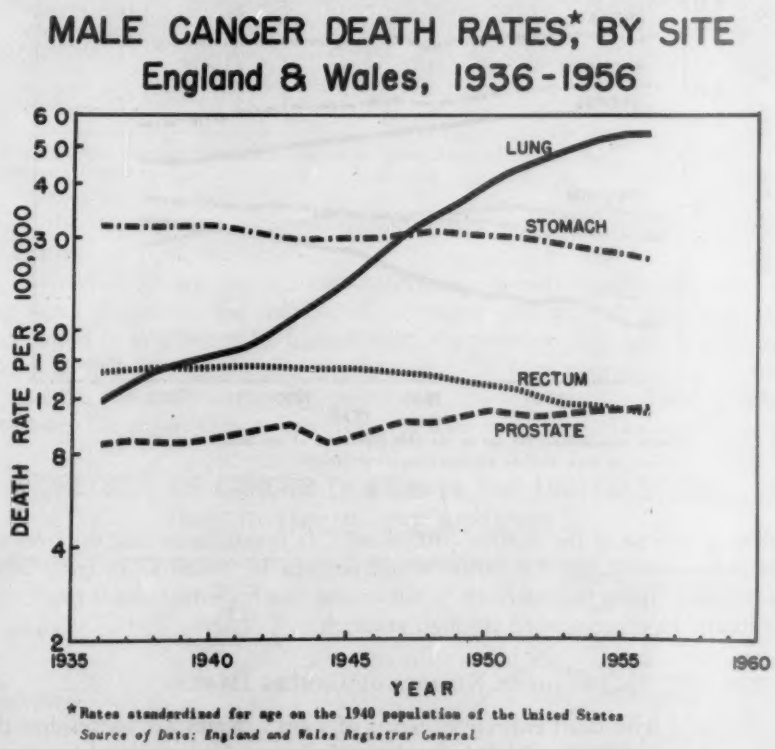

FIG. 7.

term "treatment" here being used to cover all aspects of medical care. There is also evidence that early diagnosis contributed somewhat to the over-all improvement in survival rates.

There is every reason to believe that cancer survival rates for the population as a whole can be improved still further by more effective utilization of present knowledge. This could be accomplished (1) through professional education to bring the average level of professional care up to the level of the very best that is now being accomplished by leaders in the field, and (2) through earlier diagnosis. The latter requires the coöperation of the

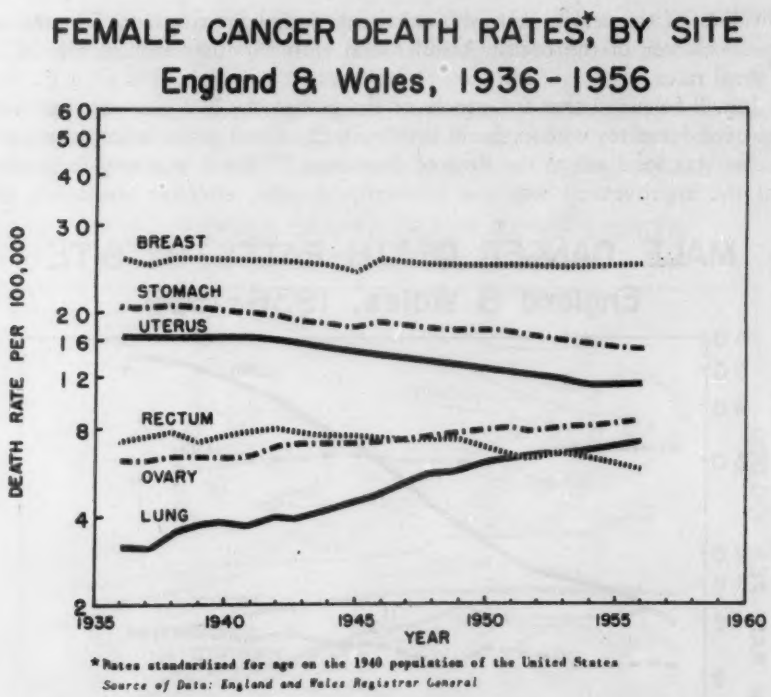

FIG. 8.

public as well as of the medical profession. It is estimated that the over-all five-year survival rate for cancer could perhaps be raised to roughly 50% by means of these two methods.[3] Of course, we hope that much more will eventually be accomplished through research.

TRENDS IN NUMBER OF CANCER DEATHS

So far I have dealt entirely in terms of rates. Rates are useful, but the extent of the medical problem—the demands for medical care and for facilities to handle patients—depends upon the absolute number of cases. Like-

TABLE 1

Five-Year-Survival Rates for All Sites of Cancer Combined, by Sex; Connecticut, 1935–1940, 1941–1946, 1947–1951

Period	Male	Female	Total
1935–1940	19%	29%	25%
1941–1946	22%	35%	29%
1947–1951	25%	38%	32%

Source: Reference 4.

TABLE 2

Five-Year-Survival Percentages for Cancer of Selected Sites by Stage, for Two Periods

Site	Localized		Regional Involvement		All Stages	
	1935–1940	1947–1951	1935–1940	1947–1951	1935–1940	1947–1951
Colon	24	48	10	30	13	29
Rectum	17	43	9	25	12	25
Cervix uteri	45	65	26	33	35	53
Corpus uteri	56	69	—†	—†	48	62
Prostate	18	25	—†	22	12	21
Breast	65	66	31	37	41	46
Bladder	28	40	—†	—†	23	31
Stomach	7	13	4	5	4	6

† Insufficient number of cases available for computing reliable rates.
Source: Reference 4.

wise, the impact upon society depends in large measure upon the number of deaths.

As is well known, cancer death rates increase very rapidly with advancing age. Therefore, the number of new cases (or deaths) occurring in a population in any one year depends upon the number of people in each age group as well as upon the age specific rates. In most countries the average age of the people is advancing, and in the United States and many other countries the population is increasing as well as aging. The size and age

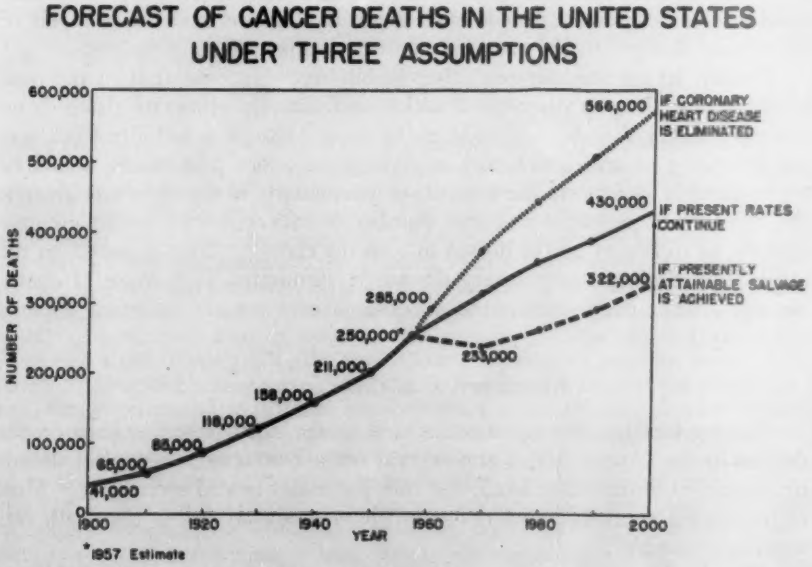

FIG. 9.

distribution of the population in age group 30 and above can be predicted for several decades into the future with reasonable accuracy, provided mankind neither suffers a great calamity nor discovers a marvelous new way of reducing death rates. Subject to such unforeseen events, it is apparent that the adult population of the United States will continue to increase in numbers and grow older for the next 40 or 50 years. This means that the number of new cases of cancer occurring each year will almost certainly continue to increase (unless we are able to prevent the disease).

Figure 9 shows the number of cancer deaths which have been reported each year in the United States from 1900 up to the present time. Also shown are estimates of future trends under three different assumptions.

First, let us assume that age-specific death rates from cancer and all other causes remain exactly as they are today. In that event the annual number of cancer deaths will increase, as shown by the thin solid line on the chart. The sole reason for the increase under this assumption is the growth and aging of the population. Roughly 430,000 Americans would die of cancer in the year 2000.

Next, let us assume (1) that in the course of the next dozen years we succeed in raising the cancer five-year survival rate from about one third, as at present, to about one-half, as seems possible with present knowledge, but (2) no wonderful new cure is found for cancer, and (3) age-specific death rates from all other causes remain as they are today. Under these conditions the annual number of cancer deaths would drop slightly for a few years, as shown by the broken line on the chart. However, the annual number of cancer deaths would then begin to increase again as a result of continuing changes in the size and age distribution of the population.

Finally, let us consider one other possibility. Suppose that in the near future a new drug is discovered which will entirely eliminate death from coronary artery disease. This is no more fantastic a possibility than was the discovery of antibiotics such a short time ago. The result would be a considerable increase in the population, particularly in the older age groups. With more old people, the annual number of cancer deaths would increase sharply, as indicated by the dotted line on the chart. (This is based on the assumption that coronary artery disease is eliminated as a cause of death, but age-specific death rates from all other causes remain the same as they are today.)

Summary and Conclusions

Among females, the age-standardized cancer death rate has been on the decline in the United States and several other countries for the last decade or longer. On the other hand, the rate for males is still increasing. Most of this increase among males is due to the phenomenal rise in the death rate from lung cancer.

The death rate from cancer of the uterus is declining quite rapidly in

this country, presumably as a result of control activities. The death rate from stomach cancer is declining, apparently as a result of a decline in incidence rates. The reason for this is unknown.

There is evidence that the five-year survival rate for cancer has markedly improved during the past decade or two. The greatest improvement has apparently occurred for cancer of the colon, rectum, cervix uteri, corpus uteri, prostate and, to a lesser degree, cancer of the bladder.

It is estimated that about one third of those who develop cancer in the United States today will be five-year survivors, this being a considerable improvement over the one quarter being saved a decade or two ago.

Unless some practical method of prevention is discovered and applied, the annual number of new cases of cancer per year in the United States will almost certainly rise steadily during the next 50 years as a result of the growth and aging of the population. This means that the need for medical care as well as facilities for cancer patients will inevitably increase. On the other hand, there is reason to believe that the cure rate can be improved (perhaps up to as high as 50%) by more effective use of present knowledge for the detection, diagnosis and treatment of cancer. This can be achieved only through the coöperative efforts of practically all branches of the medical profession. It is also apparent that effective application of preventive measures, as they are discovered by research, will depend upon the combined efforts of the medical profession as a whole.

Acknowledgments

The author wishes to thank Mr. Herbert Seidman and Mrs. Constance Percy for assistance in preparing this material. Some material assembled by Dr. Mitsuo Segi was forwarded by Mr. William M. Haenszel.

Summario in Interlingua

Le crude mortalitate ab cancere cresce continuemente in le majoritate del paises. Isto resulta primarimente ab le facto que le etate medie del population in quasi omne partes del mundo cresce in consequentia de meliorate superviventias probabile e in consequentia de alterationes del natalitate. Le mortalitate ab cancere, in su forma standardisate pro le etate, ha descendite pro femininas durante le passate decennios in le Statos Unite, Anglaterra e Galles, Switza, e certe altere paises. Le mortalitate ab cancere, in su forma standardisate pro le etate, ha crescite pro masculos in le Statos Unite e in Anglaterra e Galles. Isto resulta ab le rapidissime augmento del mortalitate ab cancere pulmonar. Post excluder cancere pulmonar, le mortalitate ab cancere, in su forma standardisate pro le etate, ha crescite levemente pro masculos in le Statos Unite e ha descendite levemente pro masculos in Anglaterra e Galles. Le mortalitate ab cancere del stomacho, in su forma standardisate pro le etate, ha descendite depost alicun annos pro masculos e femininas in le Statos Unite e in Anglaterra e Galles. Le ration que explica iste descendita non es cognoscite.

In le Statos Unite il ha occurrite un melioration considerabile del superviventia cinquenne de patientes con cancere. Le plus marcate melioration pare haber occurrite pro cancere del colon, del recto, del cervice del utero, del corpore del utero, del prostata, e—minus frappantemente—del vesica. Es estimate que circa un tertio de omne le patientes currentemente sub tractamento pro cancere in le Statos Unite va

superviver cinque annos o plus, durante que alicun decennios retro le superviventia cinquenne amontava a solmente 25%. Si omne patientes con cancere recipeva le melior curatela medical que es hodie disponibile e si nos poteva utilisar maximalmente le cognoscite methodos pro le detection de cancere in stadios precoce, le superviventia cinquenne poterea possibilemente esser avantiate a 50%.

Excepte si un nove e plus efficace methodo therapeutic es trovate, le numero annual del mortes ab cancere in le majoritate del paises va continuar crescer durante le veniente decennios a causa del augmento del populationes e del augmento del etate medie del humanos.

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THE RED CELL INDICES IN THE DIAGNOSIS OF IRON-DEFICIENCY ANEMIA *

By Ernest Beutler, M.D., *Chicago, Illinois*

It has been recognized for many years that patients with hypochromic microcytic anemia usually respond to iron therapy.[1] Conversely, it has usually been assumed that iron deficiency always causes a hypochromic microcytic anemia. Thus, it has been stated authoritatively that "hypochromic microcytic anemia . . . is the only type of anemia in which such treatment [iron] is clearly effective." [2] More recently, it has been found that iron-sensitive anemias are also characterized by the absence of stainable iron in the sternal marrow,[3] and often by reduction of the plasma iron concentration in association with an increase in the iron-binding capacity of the serum.[4]

In a recent study we used these technics in an investigation of a large number of anemic patients.[5] In the current report we examined the red cell indices of these and other patients to determine how reliable the presence of hypochromia and microcytosis was in diagnosing iron deficiency. Although we confirmed the classic concept that severe iron deficiency anemia is almost always hypochromic and usually microcytic, we also found that the milder, perhaps more common form of iron-deficiency anemia was not invariably hypochromic or microcytic. This finding is regarded as important because, prior to these studies, we did not entertain the diagnosis of iron deficiency in patients who suffered from abnormal fatigue, headaches, dyspnea and other symptoms of the iron-deficiency state and who had a mild normochromic, normocytic anemia. Such a clinical picture is exceedingly common in our experience, but, like many other physicians, we regarded these patients as psychoneurotic individuals whose hemoglobin values rested, by chance, in the lower tail of the normal distribution curve.

Materials and Methods

A. *Patients:* All patients were seen in the out-patient clinics or the hospitals of the University of Chicago Clinics. Included in the study are all adults with iron-deficiency anemia seen by the author in the two-year period ending in December, 1957, who had a clearly adequate response to iron therapy and in whom hemoglobin, red count and hematocrit determinations had been carried out in one of two reliable clinical laboratories at the Uni-

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From the Argonne Cancer Research Hospital, USAEC, and The Department of Medicine, The University of Chicago.

Requests for reprints should be addressed to Ernest Beutler, M.D., Assistant Professor of Medicine, The University of Chicago, Chicago 37, Illinois.

versity of Chicago Clinics before treatment was initiated. In most cases the diagnosis of iron deficiency was also substantiated by examination of the sternal marrow for iron and/or determination of plasma iron and iron-binding capacity.[5]

Excluded from the study were:

1. Individuals with malabsorption syndromes.
2. Individuals who had undergone splenectomy.
3. A few subjects in whom repeated blood counts prior to treatment gave markedly inconsistent results.

Control subjects without hematologic disease were selected only on the basis of availability of adequate blood counts.

B. *Peripheral Blood Counts:* Blood samples were obtained either from the finger or by venipuncture, using heparin as the anticoagulant. The hemoglobin concentration of the blood was measured spectrophotometrically as alkaline oxyhemoglobin. The standard curve was determined from samples the hemoglobin content of which had been measured both by the cyanmethemoglobin method against College of American Pathologists standards, and blood samples the hemoglobin content of which had been determined by the oxygen capacity method. The calibration of all pipets was checked with dye. Red blood counts were carried out using Thomas diluting pipets which had been certified by the National Bureau of Standards, or which had been calibrated by the manufacturer and stated to be correct within 1% of the given dilution. At least five 0.02 mm. squares in a counting chamber were counted.* Hematocrit determinations were carried out using Wintrobe hematocrit tubes or the microhematocrit method. Extensive comparison of these hematocrit methods in our laboratory [6] and by others [7] has indicated that the results are virtually identical.

The mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and the mean corpuscular hemoglobin concentration (MCHC) have been calculated in the usual manner.[8]

C. *Blood Smears:* Blood smears were made on glass microscope slides and were stained with Wright's stain. Sixteen such slides were labeled only by number. Included in this collection were six slides made from five patients without hematologic disorders and with normal red cell indices, six slides made from five patients with iron-deficiency anemia whose red cell indices were normal, and four slides from iron-deficient patients with abnormal red cell indices. The sole criterion for selection of these slides was their availability.

The collection of slides, each identified only by number, was examined by the following observers:

* Since this study was completed, red cell counts in these laboratories have been checked using an electronic red cell counter (a modified Coulter Counter, Model A131). Excellent agreement has been obtained.

Observer No. 1: Clinical hematologist. Director of a leading hematologic research laboratory.

Observer No. 2: Clinical hematologist. Professor of medicine.

Observer Nos. 3 and 4: Clinical hematologists. Assistant professors of medicine.

Observers Nos. 5, 6 and 7: Registered technologists. Supervisors in hematology laboratories at major teaching and research institutions, each with many years' experience in hematology.

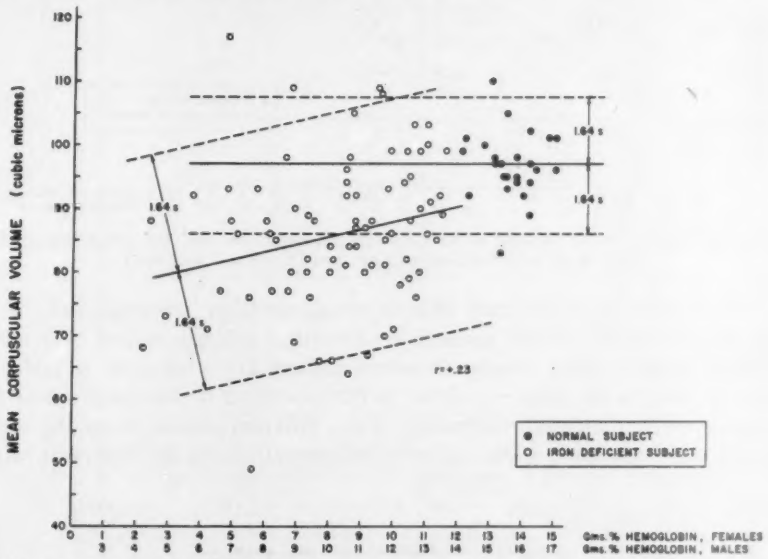

FIG. 1. The relationship between mean corpuscular volume and the blood hemoglobin level of 80 iron-deficient patients and 25 normal subjects.

RESULTS

The red cell indices of 80 iron-deficient patients and 25 normal subjects are presented in figures 1, 2 and 3. If we assume that the normal values follow a Gaussian distribution, only 5% of the normal values should fall below the lower horizontal broken line in these figures. It is apparent that the red cell indices of many of the iron-deficient subjects are well below the normal range; this is particularly true in the more anemic patients. The range in which 90% of the red cell indices would be expected to fall at each hemoglobin level has been indicated by the diagonal broken lines.* It is apparent, however, that at hemoglobin levels of over 7 gm. for females and 9 gm. for males, substantial numbers of patients have normal red cell indices.

*The regression equation and its standard deviation have been calculated by the usual technics.[9]

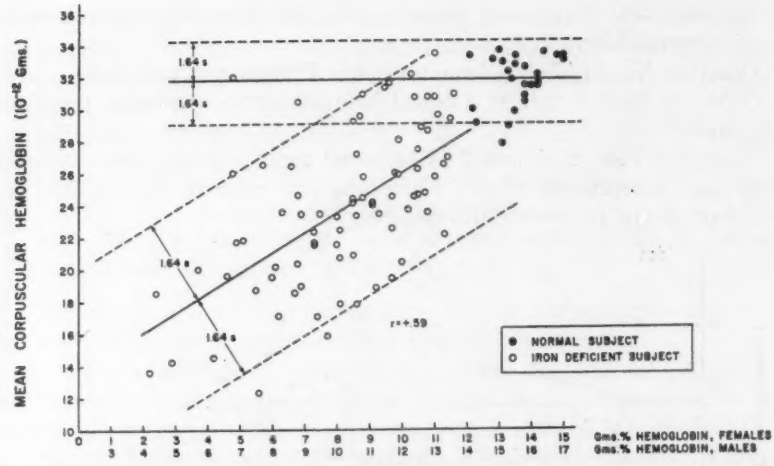

FIG. 2. The relationship between mean corpuscular hemoglobin and the blood hemoglobin level of 80 iron-deficient patients and 25 normal subjects.

The results of examination of stained smears from hematologically normal subjects, iron-deficient patients with normal red cell indices, and iron-deficient patients with clearly abnormal indices are presented in table 1. Most striking is the great variation in interpretation of the same smear by a number of experienced observers. Even different smears from the same subject were frequently given different interpretations by the observers who,

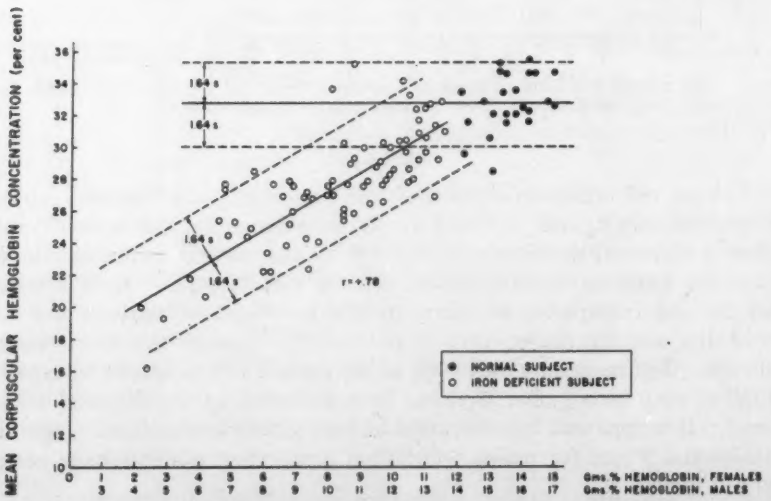

FIG. 3. The relationship between mean corpuscular hemoglobin concentration and the blood hemoglobin level of 80 iron-deficient patients and 25 normal subjects.

TABLE 1

Seven Observers' Interpretations of 17 Blood Smears from 15 Patients

Diagnosis	Patient	Hb. Gm.%	MCV cu. μ	MCH 10^{-12} gm.	MCHC %	Observer														Fraction of Observers Detecting Abnormality
						No. 1		No. 2		No. 3		No. 4		No. 5		No. 6		No. 7		
						Hyp.*	A or P†	H	A or P	H	A or P	H	A or P	H	A or P	H	A or P	H	A or P	
No hematologic disease	Mr. S. Slide 1	—	—	—	—	0	0	0	0	0	0	0	0	0	+	0	0	0	0	
	Mr. S. Slide 2	—	—	—	—	+	+	0	+	0	0	0	0	0	0	0	0	0	0	
	Mrs. E. C.	13.8	98	31.4	32.1	0	+	0	0	0	0	0	0	0	0	0	0	0	0	
	Mrs. H.	14.2	89	31.6	35.5	0	+	0	++	0	0	0	++	0	0	0	+	0	0	
	Mr. R. A.	15.3	97	32.3	33.3	0	0 +	+	+	0	0	0	0	+	0	0	0	0	0	
	Mr. W.	14.2	101	30.0	29.6	0	+	0	++	0	0	0	0	0	+	0	+	+	+	
Iron deficiency, normal indices	Mrs. B.	8.8	88	31.0	35.0	0	++	0	++	0	±	0	+	0	+	0	+	+	+	2/7
	Mrs. C.	11.6	99	30.9	31.0	0	+	+	++	0	0	0	+	0	0	0	++	0	0	1/7
	Mr. H.	13.0	103	33.4	32.5	0	0	++	+	++	±	±	0	++	0	±	+	0	0	5/7
	Mrs. E. D.	11.1	91	29.6	32.7	++	++	+	+	±	0	+	+	0	0	0	0	+	+	3/7
	Mrs. D. Slide 1	10.4	99	30.7	30.5	0	++	0	++	++	++	+++	++	+++	0	0	++	+	++	6/7
	Mrs. D. Slide 2	10.4	99	30.7	30.5	+	++	0	++	±	++	±	+	0	+	0	+	+	++	4/7
Iron deficiency, abnormal indices	Mrs. F.	8.6	84	23.3	27.7	++	++	++	+	±	++	++	+++	+	0	+	++	++	+++	6/7
	Mrs. G.	7.3	80	21.5	27.0	+++	+++	+++	+++	++	+++	+++	+++	+++	++	+	++	+++	+++	7/7
	Mrs. R.	8.8	92	24.4	25.9	+	+	+	+	0	±	0	0	+++	++	+++	+	+	+	2/7
	Mr. R. I.	8.8	109	30.4	27.9	0	+	+++	++	±	++	++	++	+	++	0	+	0	0	4/7

* Hypochromasia.
† Anisocytosis or poikilocytosis.
Scores greater than the observer's "threshold" of abnormality are underlined.

of course, did not know that they were examining duplicate smears. None of the seven observers was willing to call all of the normal smears entirely normal. If we adjust upward the "threshold" for abnormality to the highest grade given by a particular observer to a normal smear, none of the observers was able to detect anisocytosis, poikilocytosis or hypochromia in all of the iron-deficient patients with normal red cell indices. One observer identified only one of the six smears as abnormal. Only two of the five patients were identified as abnormal by more than half of the observers. While the fact that some smears from patients with normal red cell indices were identified as abnormal might suggest that examination of the smear was a more adequate means of making a diagnosis of iron deficiency than are the red cell indices, it is interesting to note that only three out of the seven observers were able to detect abnormalities in one of the four patients with iron-deficiency anemia who had clearly abnormal red cell indices.

Discussion

It has been recognized previously that the degree of hypochromia and microcytosis in iron-deficiency anemia varies directly with the degree of anemia. In an early study, Wintrobe [10] correlated the hemoglobin values of 21 patients with idiopathic hypochromic anemia with many determinations of their MCV and MCHC. He found that the regression equations were $MCV = 2.6\ Hb + 45$, and the $MCHC = 1.04\ Hb + 19.2$. In spite of this clear dependence of the degree of hypochromia and microcytosis on the degree of anemia, it has been suggested only rarely that the red cell indices might be in the normal range in some patients with iron-deficiency anemia.[5, 11] Indeed, some clinical hematologists have told me that they have never seen a patient with iron deficiency who had normal red cell indices. The terms "iron-deficiency anemia" and "hypochromic anemia" are often used quite synonymously.

Rigid adherence to the concept that all patients with iron deficiency have abnormal red cell indices will result in a failure to diagnose a sizable proportion of patients with iron-deficiency anemia (see case report). The patients in whom the diagnosis will be missed will usually be the ones with a milder degree of anemia. However, as Heilmeyer and Plötner [12] pointed out long ago, and as we have recently emphasized,[13] the symptoms of iron deficiency probably do not arise from the anemia alone. Hence the failure to diagnose this deficiency state, even in its milder forms, may result in much unnecessary fatigue and discomfort to a patient who could be treated easily.

The mean values for the normal red cell indices that we have reported in this study are essentially identical with the results of Walters,[14] Freedman and Mirsky [15] and Johnson.[16] The normal range for red cell indices given by Wintrobe [17] and other investigators [18, 19, 20, 21] differs somewhat from those reported by the above authors, and those found in the present series. Such discrepancies are probably the result, as has been suggested by Wintrobe,[17]

of differences in method. Since the values obtained in our laboratories are internally consistent, such differences should in no way detract from the validity of the results when they are considered in the frame of reference provided by our own normal values.

It is our opinion that determination of the red cell indices should be the starting point for the investigation of an anemia. Examination of the red cells on a peripheral blood smear is also essential. However, it is important to recognize that the diagnosis of iron deficiency should not be excluded on the basis of either normal red cell indices or normal red cell morphology on the smear. When their bone marrow contains no stainable iron, patients with mild normochromic normocytic anemias will usually be benefited markedly by administration of iron. It is sometimes necessary to continue oral administration of iron for several months to obtain a satisfactory response, and occasionally parenteral iron may be required. This is in contrast with the more rapid response of severely anemic iron-deficient patients, and may explain, in part, the frequent failure to recognize the existence of this type of iron-deficiency anemia.

Summary

1. The red cell indices of 80 patients with iron deficiency have been measured.

2. Most of these patients' red cell indices indicated the presence of hypochromia and microcytosis, but among the less severely anemic patients, normal red cell indices were common.

3. On examination of stained smears, experienced observers were able to detect abnormalities of the red cells of some of these subjects, but no observer was able to detect abnormalities in all of them. The same observers missed abnormalities on smears from some patients whose red cell indices clearly indicated the presence of hypochromia and microcytosis. Examination of stained smears was therefore not clearly superior to determination of red cell indices.

4. It is concluded that, while determination of red cell indices and examination of stained smears are important, one cannot exclude the diagnosis of iron deficiency on the basis of normal red cell indices or normal appearance of red cells on the smear alone. This is particularly true in the case of mildly anemic patients.

Case Report

Mrs. D., a white housewife, was first seen by the author in October, 1952, when she was 46 years of age. She complained of fatigue, headache and dizziness of two or three years' duration. Past history revealed that a partial thyroidectomy had been carried out as treatment for thyrotoxicosis at the age of 22. On physical examination, the left lobe of the thyroid was palpable and the liver was felt 5 cm. below the costal margin. The nails on the hands and feet were thin, hard and concave, and extensively ridged. The skin was dry and pale. The hemoglobin was 11.8 gm.%,

and the red count was 3.76 million per cubic millimeter. One month later, the hemoglobin was found to be 10.9 gm.%, the red cell count, 3.42 million. The diagnosis of iron deficiency was not entertained, and it was thought that the patient suffered from hypothyroidism. The protein-bound iodine was reported to be 0.7 μg.%. The serum cholesterol, however, was normal, and the basal metabolic rate was plus 6.

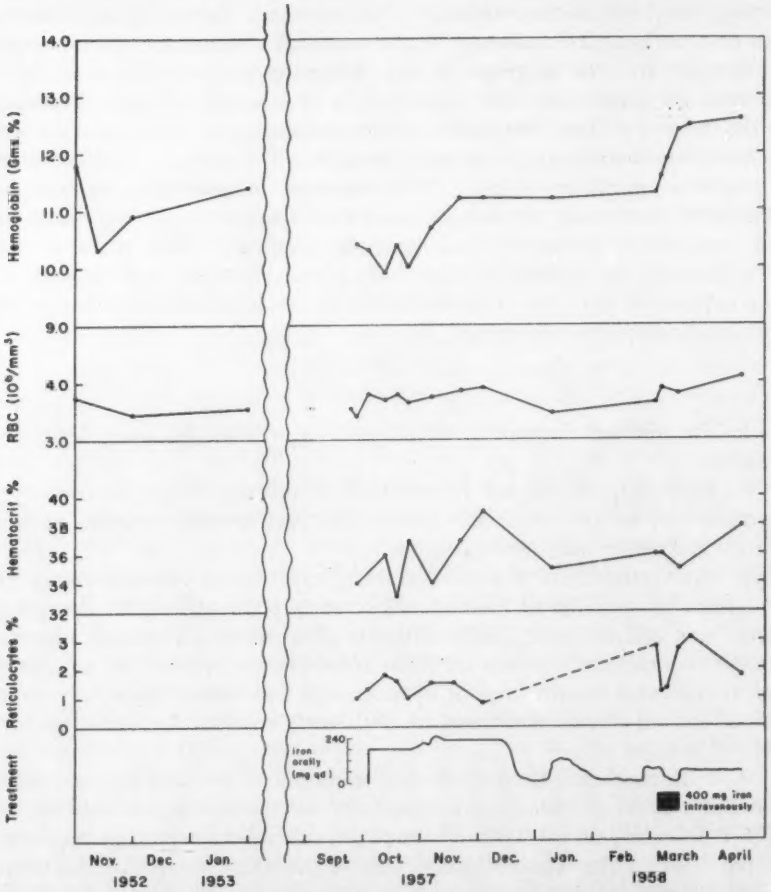

FIG. 4. The effect of iron therapy on the hemoglobin, red count, hematocrit and reticulocyte count of case 1.

The protein-bound iodine was repeated and found to be 3.6 μg.%. The patient was seen in consultation with an endocrinologist, and a trial on thyroid therapy was recommended. This failed to affect appreciably either the anemia or the other symptoms. Having received no symptomatic relief from this therapy, the patient failed to keep her return appointments and was not seen again until September, 1957. At this time, having been seen in Dermatology Clinic because of mild psoriasis, she was persuaded to return to the author's care. At this time her hemoglobin was 10.4

gm., red count, 3.38 million, and hematocrit, 34%. Physical examination revealed that her condition was essentially unchanged except for a slight swelling of interphalangeal joints. This was regarded as probably representing mild psoriatic arthritis or osteoarthritis. Sternal bone marrow examination revealed a complete absence of stainable iron, and the plasma iron was found to be 30 μg.%, with an unsaturated iron-binding capacity of 375 μg.%. Oral iron therapy was started with ferrous sulfate on October 2, 1957, and blood counts were repeated at frequent intervals. The findings are presented in figure 4. In one month there was no appreciable change in the peripheral blood counts, but the patient stated that she felt better than she had for two or three years. Her hemoglobin gradually rose, but because of poor gastrointestinal tolerance for iron, she began to take iron only intermittently. Between March 5, 1958, and March 14, 1958, a total of 400 mg. iron was given intravenously as saccharated iron oxide. A prompt additional rise in the hemoglobin occurred. Oral therapy is being continued indefinitely in the form of ferroglycine sulfate (Ferronord), which appears to be better tolerated by the patient than is ferrous sulfate.

SUMMARIO IN INTERLINGUA

Il es ben cognoscite que patientes con anemia microcytic hypochromic responde usualmente al therapia a ferro. Inversemente, on ha sovente supponite que un anemia a carentia de ferro es semper hypochromic e microcytic.

Pro determinar si o non iste supposition es correcte, le volumine corpuscular medie, le hemoglobina corpuscular medie, e le concentration medie de hemoglobina corpuscular esseva estimate in le casos de 80 patientes con carentia de ferro e in 25 subjectos con normal characteristicas hematologic. In plus, frottis de sanguine ab certes de iste individuos esseva examinate per septe experte observatores: quatro hematologos clinic e tres technicos.

Le carentia de ferro es determinate per le absentia de ferro tincturabile in le medulla sternal e frequentemente per le reduction del concentration de ferro in le plasma in association con un augmento del potentia ferro-ligatori del sero.

Le resultatos del hic reportate studios indica, durante que hypochromia e frequentemente etiam microcytosis esseva usualmente presente in patientes con sever grados de anemia, que indices erythrocytic de valor normal es un constatation commun in subjectos con leve formas de anemia a carentia de ferro. Le conclusion del studios es que le determination del indices erythrocytic e le examine de tincturate frottis de sanguine es importante sed que il non es permissibile excluder le diagnose de carentia de ferro super le base de normal indices erythrocytic e del apparentia normal del erythrocytos in le frottis de sanguine. Es presentate un caso que illustra le responsa al therapia a ferro in un patiente con carentia de ferro e normal indices erythrocytic.

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BASAL SYSTOLIC MURMURS AND THE CAROTID PULSE CURVE IN THE DIAGNOSIS OF CALCAREOUS AORTIC STENOSIS * †

By GEORGES DAOUD, M.D., EDMUND H. REPPERT, JR., M.D., and J. SCOTT BUTTERWORTH, M.D., F.A.C.P., *New York, N. Y.*

WE have reviewed the last 30 autopsies at the University Hospital in which the diagnosis of calcareous aortic stenosis was made by the pathologist. Somewhat to our surprise we found that the clinical diagnosis had been missed in 65% of the cases, although we should have expected this from the literature [1, 2, 3] and our own studies.

The literature reveals many opinions concerning calcareous aortic stenosis. For instance, the etiology has been variously ascribed to a primary degenerative arteriosclerotic lesion,[4, 5] to rheumatic fever,[2, 6, 7] to congenital anomalies [8] and to hypercholesterolemia.[9, 10]

The typical case presents a history of a systolic murmur known for many years, during which the patient is asymptomatic. This is followed by a period of increasing, variable symptomatology, including fatigue, sweating, dyspnea, orthopnea, chest pain, dizziness and syncope. Death is usually sudden, or due to congestive heart failure with or without acute or subacute bacterial endocarditis. Moreover, once the disease becomes symptomatic, the prognosis is unfavorable, and with the development of congestive heart failure and/or angina pectoris the life expectancy is short.[20] The disease is three times more frequent in males, is more common over the age of 50 years, and is uncommon in Negroes. While the clinical picture is frequently helpful in leading one to suspect aortic stenosis, it may be difficult to differentiate aortic stenosis from chronic coronary artery disease in older people.

It is the purpose of this communication to consider the physical and laboratory features diagnostic of calcareous aortic stenosis, to point out some of the difficulties encountered, and to describe and evaluate a new method of recording the carotid pulse.

The features usually considered to be most helpful in diagnosis are the variations in the blood pressure, evidence of left ventricular hypertrophy in the electrocardiogram and by x-ray, calcification of the valve determined by fluoroscopy, and the auscultatory findings.

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From the Division of Cardiology, University Hospital, The Postgraduate Medical School of New York University-Bellevue Medical Center, New York, N. Y.

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Requests for reprints should be addressed to J. Scott Butterworth, M.D., University Hospital, 303 E. 20th St., New York, N. Y.

Blood Pressure: Aortic stenosis has been considered to be associated with a low systolic pressure and a low pulse pressure,[11] but hypertension has been reported [1, 12] in from 10 to 29% of cases.[13, 14] We have seen cases with blood pressures as high as 260/110 mm. of Hg. Frequently the diastolic pressure is lower due to associated aortic insufficiency. This makes the diagnosis and grading of aortic stenosis by pressure values of limited value, as pointed out by Kumpe and Bean.[12, 15]

Electrocardiogram: The most common finding in the electrocardiogram is that of left ventricular hypertrophy or strain, although conduction disturbances are common, and one may see combinations of hypertrophy and ischemia or infarction. We have seen cases where the electrocardiogram was so distorted by previous myocardial infarction that the pattern of left ventricular hypertrophy was not readily apparent. Occasionally the electrocardiogram will show little or no evidence of left ventricular hypertrophy, even with moderately severe aortic stenosis.[16] Atrial fibrillation is uncommon unless there are associated lesions involving the mitral valve.

X-Ray: The chest x-ray will usually reveal the boot-shaped heart of left ventricular hypertrophy, but not infrequently (particularly with vertical positions of the heart) the cardiac silhouette appears to be within normal limits. Calcium may occasionally be seen, but is much better visualized by fluoroscopic examination.

Fluoroscopy: The demonstration of calcium in the aortic valve is of great diagnostic help.[17, 18] It must be emphasized that, in looking for calcium within the heart, excellent dark adaptation must be accomplished, which usually requires at least 15 minutes. Calcium in other valve areas, such as the mitral, may be confusing but can usually be differentiated by the configuration and motion of the calcium. Of course, some degree of aortic stenosis may be present with little calcium deposited within the valve.

Auscultation: The classic features are a loud, rough systolic murmur localized in the second right interspace, transmitted well to the carotid vessels and accompanied by a thrill. The second aortic sound may be diminished or absent. A murmur of aortic insufficiency may also be present. The systolic murmur is frequently of such intensity that it is transmitted widely and may be heard over the entire chest as well as the skull and bony prominences of the shoulder and elbow.[19]

Unfortunately, however, many factors influence the production and transmission of these murmurs, and not infrequently the murmur at the aortic area may be insignificant. This is particularly true in emphysema, with fast heart rates, in shock, in cardiac failure, and in some cases of mitral stenosis. With atrial fibrillation or other arrhythmias the intensity of the murmur is usually proportional to the time of diastolic filling, and the shorter the period of diastolic filling, the less intense the murmur becomes.

It has been reported [20] that in the presence of associated significant aortic insufficiency the murmur of aortic stenosis may be increased in intensity,

and we have noted that some of our loudest murmurs do indeed occur in patients with combined aortic stenosis and insufficiency.

While the murmur generally has greatest intensity at the aortic area, we have seen many verified cases where the murmur was loudest or was heard only at the left sternal border or at the apex.[21] The variations in location and intensity from person to person may be related in part to varying positions of the heart in the thoracic cage.

At other times the murmur may be high-pitched and musical, with a squeaking quality;[22] and again, the location of maximal intensity may be quite variable, so that the condition may be confused with mitral insufficiency or other lesions.

The aortic component of the second sound is frequently diminished or absent in severe grades of aortic stenosis. This has been related to the immobility of the valve cusps due to calcification. This diminished aortic second sound has been emphasized by Austin Flint,[23] and has been accepted as good evidence of aortic stenosis and its absence as a safe indication of the absence of severe stenosis.[7, 12] However, this is not invariably true, and some of our advanced cases have had very loud aortic components of the second sound. It should be noted that it is difficult by auscultation alone to distinguish between a loud aortic component and a loud pulmonic component of the second sound, such as may occur if mitral stenosis is also present.

We have seen several cases of calcareous aortic stenosis presenting a history of a systolic murmur for many years which had been considered a "functional murmur." Several reports [24, 25, 28] caution about this "functional murmur" of young people without symptoms or abnormal findings which, as years pass, may develop into the full-blown picture of calcareous aortic stenosis. We do not know of any positive way to solve this problem in its infancy, but careful studies of the character of the murmur over a period of time, along with other laboratory procedures, may be fruitful. It is our practice to follow these people at intervals with tape recordings of the murmur and simultaneous recordings of the electrocardiogram, the carotid pulse, and stethograms from two or more areas.

Because of the rather marked variations of many of the physical and laboratory findings in calcareous aortic stenosis, as mentioned above, we have become interested in the correlation of the phonocardiogram and the carotid pulse tracing with these findings.

Phonocardiogram: Phonocardiographic studies individualize the systolic murmur of aortic stenosis as a diamond-shaped [26] or midsystolic murmur.[27] It begins a short time after the end of the first heart sound (sometimes just preceded by an aortic systolic ejection sound),[29] increasing to maximal intensity at midsystole and ending shortly before the aortic component of the second sound. Moreover, the studies of Leatham [27] have demonstrated that when the murmur of aortic stenosis is transmitted to the apex, the murmur retains its timing and midsystolic accentuation. In severe cases of

aortic stenosis the maximal intensity of the murmur tends to be closer to the second sound. Due to the prolonged left ventricular contraction as a result of the aortic stenosis, the aortic component of the second sound has been reported to be delayed over the pulmonic component (paradoxic splitting).[30] In our experience, the delayed aortic component has not been noted too frequently, since the intensity of the sound is so diminished that it is difficult to identify.

The diamond-shaped murmur is not pathognomonic of aortic stenosis. Since it is an ejection murmur, it may also be heard in coarctation of the aorta, Ebstein's disease, pulmonic stenosis, some ventricular septal defects and other conditions. It is said to be possible to differentiate aortic stenosis from pulmonic stenosis by Valsalva's maneuver.[31] After straining, the murmur of pulmonic stenosis regains its intensity immediately, while the murmur of aortic stenosis recovers only after a delay.

More frequent is the confusion between the murmur of mitral insufficiency and the murmur of aortic stenosis, especially when the murmur of aortic stenosis is accentuated at the left sternal border, or when the murmur of mitral insufficiency is transmitted to the aortic area. The systolic murmur of mitral insufficiency [27] is differentiated from the murmur of aortic stenosis by the fact that it starts immediately after the first heart sound, reaches its full intensity early in systole, and tends to maintain about the same intensity throughout systole, ending with the aortic component of the second sound. It has been reported that the inhalation of amyl nitrite temporarily reduces or abolishes the initial systolic murmur of mitral insufficiency, and later increases the murmurs of aortic valvular disease.[32]

Carotid Pulse Tracings: The arterial pulsations have for years been considered to be helpful in the diagnosis of aortic stenosis. Among graphic methods, the carotid or subclavian pulse waves and the brachial artery pressure curve have been used.

The studies of Feil,[33] Katz,[34, 35] Wiggers,[36] Dow [37] and others [38] have demonstrated in animals and man the characteristic alterations of the curve in aortic stenosis: (a) a slow rise, (b) a lower and deeper anacrotic notch, followed by (c) a slowly rising plateau upon which vibrations are superimposed, and (d) prolonged duration of the systolic upstroke and total systole.

Although these features of the central arterial curve in aortic stenosis have been known for years, the arterial pulse wave has not been adopted as a routine procedure in studies of aortic stenosis, due mainly to technical difficulties. The early recording apparatus utilized a pneumatic receiver, but this was difficult to operate and the results were not very consistent. The crystal microphone was more often used, and, depending upon the frequency response of the system, results have been variable. Reinhold [39] and Aravanis [40] obtained the same form described above. Smith,[41] using an electronic system with limited low frequency response, emphasized the vibra-

tions on the plateau as characteristic of aortic stenosis. Duchosal [42] reported good results using an inflated neck cuff and a differential pneumatic manometer system with optical recording. Recently, several authors have used the intrabrachial pressure curve recorded through strain gauge manometers. Goldberg [43] and associates [44] stated that this pulse contour is useful in the diagnosis of aortic stenosis, but others [45] have found it of limited value. This is evidently due to distortion of the central arterial wave by the summation of standing and reflected waves.[33] To obtain better transmission of the central pulse wave, Valsalva's maneuver has been suggested,[46, 43] or the combination of Valsalva's maneuver and injection of Priscoline.[47]

In our laboratory we have found that a simple way to record the carotid pulse wave is by using a neck cuff and recording the pulse wave through a Statham strain gauge manometer. This type of equipment is now commonly available in most catheterization laboratories, and the technic is rapid, simple and reproducible.

Technic: In brief, this method utilizes a neck cuff of a type similar to that used by Duchosal,[42] which is a small edition of a blood pressure cuff. This summates the pulsations of both carotid arteries, but individual pulsations may be recorded by a suitably anchored tambour over either artery. The neck cuff is much simpler to apply than a tambour, and results are easily reproducible, so that it is generally used unless there is a question of asymmetric pulse waves in the carotid arteries.

The neck cuff is attached by a thin-bore rigid wall plastic tubing to a Statham 23 A or D * transducer. Air is used throughout the system. Also connected to the transducer is an anaeroid manometer and a rubber hand bulb with valve for introducing slight degrees of pressure into the system.

After the neck cuff is snugly fitted around the neck, the pressure within the cuff and transducer is raised to 20 to 30 mm. Hg by the hand bulb. This causes no discomfort to the patient. The output of the transducer is fed into a carrier wave amplifier † previously nulled at 40 mm. Hg. The output of the carrier amplifier is fed to an optical galvanometer and the recording is done through a conventional camera, usually operated at a paper speed of 50 mm. per second. The volume of the air in the neck cuff, tubing and transducer is not too critical. Likewise, the carrier amplifier may be nulled at higher or lower pressures, using correspondingly higher or lower pressures in the neck cuff. The same system can be used to record pulse waves from the extremities.

Recordings are made with the patient sitting or at a 45° elevation of the head to eliminate venous waves, although these can be accentuated for study by using the supine position.

There is no easy way to standardize the height of the pulse curve, but this does not interfere seriously. In general, the height of a normal carotid

* A Statham P 23 BB transducer is even more satisfactory.
† Cambridge Instrument Co., New York, N. Y.

pulse recording by this method represents a pressure change of only about 2 mm. Hg.

Material: We have recorded 25 normal subjects of both sexes between the ages of six and 84 years, 150 patients presenting all types of cardiovascular lesions *exclusive* of aortic stenosis, and 40 patients judged to have some degree of aortic stenosis.

In all of the normals and the heterogeneous group of cardiovascular lesions the features of the carotid pulse were: (a) a rapid rise of the ascending limb, (b) an inconstant anacrotic notch, (c) a variable plateau, interrupted by (d) the incisura (figure 1).

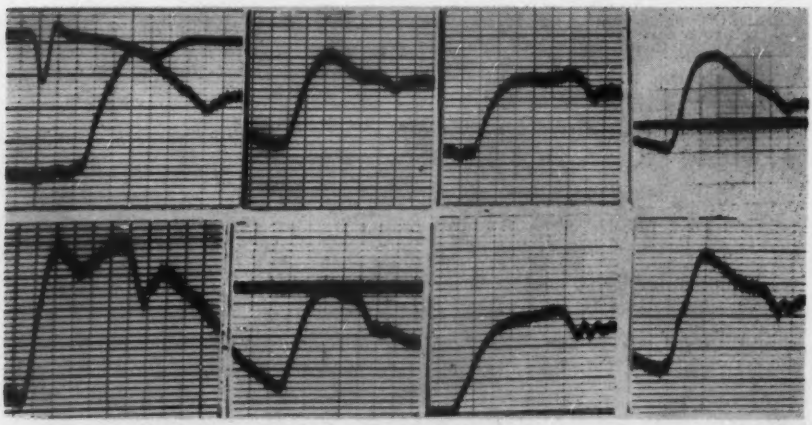

FIG. 1. Variable contours of normal carotid pulse curves as recorded by the technic described in this paper. Note the rapid upstroke, normal height and well defined incisura in all cases. The ejection angle E is less than 25°, and the ratio of ejection angle E/ systolic angle S is less than one.

We have, among other measurements, measured two angles in all curves. The angle E (figure 2), called the ejection angle, is formed by the perpendicular at the beginning of the systolic upstroke and a line tangent to the initial rise of the upstroke. In the presence of an anacrotic notch we have used the tangent to the rise preceding the anacrotic notch. This angle depends upon the rapidity of the rise of the ascending limb. The S angle, called the systolic angle, is formed by the line just described for the angle E and a line drawn from the origin of the upstroke to the incisura. In cases where the incisura was not well seen, the line was drawn from the beginning of the upstroke to a point on the curve 0.04 second after the aortic component of the second sound to compensate for the delay in the carotid pulse and the air conducted in the recording system.

Other measurements have included the systolic upstroke time and the "t" time of Duchosal [42] (figure 3). The systolic upstroke time is from the onset of the upstroke to the time of the maximal deflection. No correction

was made for cardiac rate, and this value showed wide variability—from 0.06 to 0.24 second—but the majority of the cases were well below 0.24 second. The half-time "t" of Duchosal [42] (figure 3) is the interval from the beginning of the systolic upstroke to the point on the curve located at half the amplitude of the highest point on the curve.

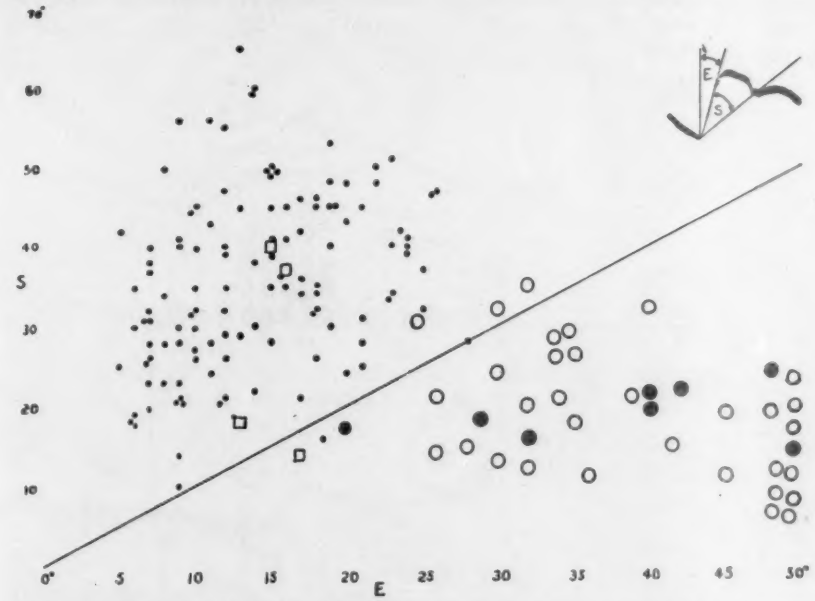

FIG. 2. The angles E and S as applied to the carotid pulse curve are indicated in the diagram in the upper right corner. The values of S in degrees are plotted in the ordinate axis, and the values of E in degrees are on the abscissa. The dots represent 25 normals and 150 cases of combined cardiovascular pathology *excluding* calcareous aortic stenosis. Squares represent cases considered to be nonhemodynamic aortic stenosis. Circles represent cases of hemodynamic aortic stenosis. The opaque circles are cases that had left heart catheterization or postmortem examination. The dividing line represents the ratio $E/S = 1$. It will be noted that, with two exceptions, all cases excluding aortic stenosis had an angle E of 25° or less, and an E/S ratio of less than one. In calcareous aortic stenosis, with few exceptions, the angle E is greater than 25° and the ratio E/S is greater than one.

Results: In all cases *excluding* aortic stenosis the angle E varied between 6° and 25°, with one exception. Angle S was always larger than E, with one exception, and hence the ratio E/S was always less than 1.

In general, we found, in agreement with Duchosal,[42] that the "t" time is normally within the range of 0.04 to 0.06 second (figure 3). However, several cases in this series, in the absence of aortic stenosis, had abnormal prolongation of the "t" time to 0.07 or 0.08 second (figure 4). This occurred mainly in hypertensive patients, but two patients of our normal group between the ages of 55 and 60 and a case of aortic aneurysm showed this abnormal prolongation.

In a few patients considered to have pure aortic insufficiency, a prolonged "t" time was also noted, although we have no absolute proof that some degree of aortic stenosis may not have been present.

In the 40 cases considered from all available historical, physical and laboratory evidence to have aortic stenosis, we found the carotid pulse curve presented the following features: (a) a slow rise of the ascending limb, (b) small to absent incisura, and (c) diminished over-all height of the curve, particularly in severe stenosis.

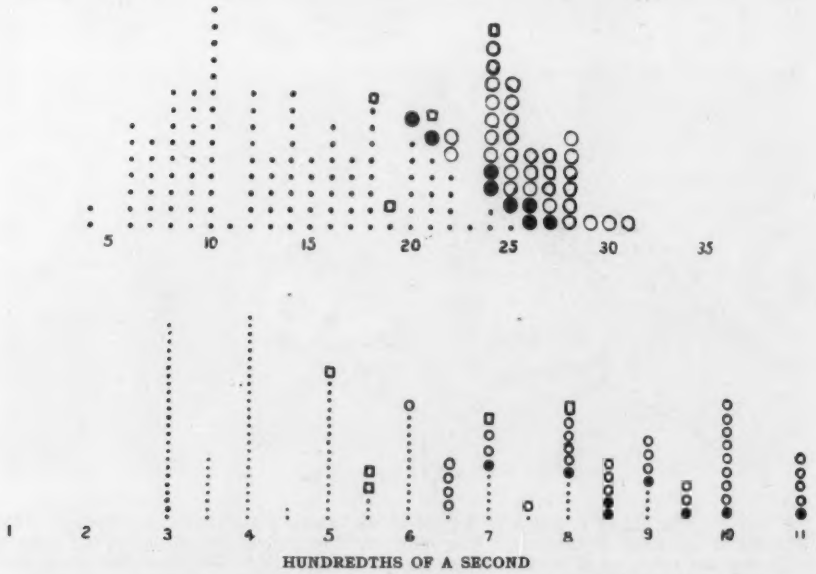

FIG. 3. The upper portion of the figure illustrates the dispersion of cases in relation to the systolic upstroke time measured in hundredths of a second. The majority of cases of calcareous aortic stenosis have a systolic upstroke time of 0.24 second or more. The lower portion of the figure shows the dispersion according to the half-time "t" of Duchosal. All cases of hemodynamic aortic stenosis have a value of 0.06 second or greater, but many cases without aortic stenosis also fall above 0.06 second. Cases are identified as in figure 2.

The ejection angle E was above 25° and in the majority of cases above 30°. The systolic angle S was decreased so that E/S was greater than unity, with three exceptions. The systolic upstroke time in cases of aortic stenosis overlapped some of the other lesions (figure 3), but in general the systolic upstroke time was greater than 0.24 second.

By our technic the anacrotic notch has not been a consistent finding, and, when present, its position and amplitude have not been helpful in the diagnosis of aortic stenosis. However, in all cases of severe calcareous aortic stenosis the anacrotic notch was absent and the incisura minimal or absent.

Vibrations on the ascending limb and plateau have not been a consistent finding. They were more often present with aortic systolic murmurs of marked intensity.

While the "t" time was abnormally prolonged in the cases of aortic stenosis, we were not able to correlate the "t" time with the severity of the stenosis (figure 3).

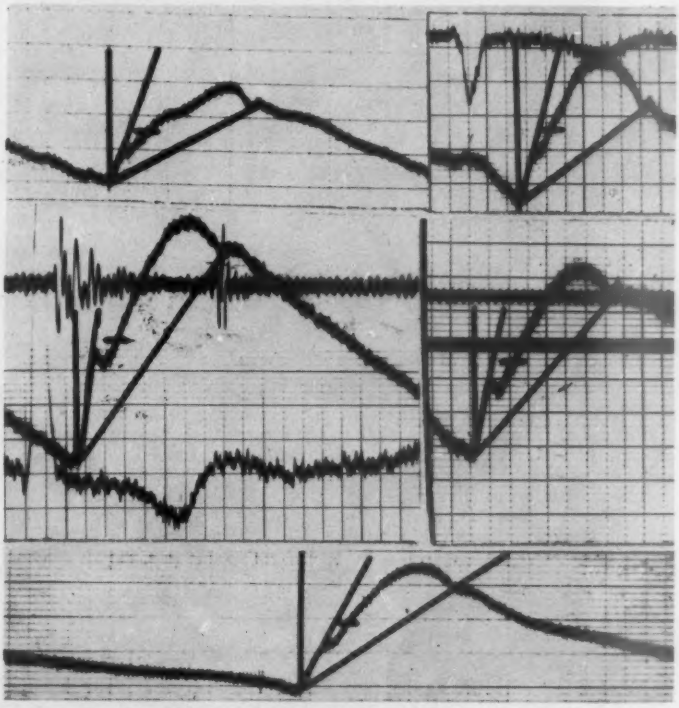

FIG. 4. Five cases without aortic stenosis illustrating the angles E and S, and also the half-time "t" which is indicated by small horizontal lines on the upstrokes. The discrepancies between angle E and the half-time "t" are readily apparent.

We have used the following classification, although we fully appreciate the difficulties of so doing.

1. *Severe Aortic Stenosis:* The ascending limb of the carotid curve presented a long delayed rise to a very late single peak (figure 5). The entire wave was of low amplitude, the incisura was minimal to absent, and the ratio E/S was greater than one. Clinically, these patients all presented evidence of severe aortic stenosis. Four patients in this group came to autopsy and showed a very tight calcareous aortic stenosis (figure 6). The aortic gradient had been determined in two of these, and was 75 mm. Hg at operation in one and 90 mm. Hg by left heart catheterization in the other.

2. *Aortic Stenosis:* In this group the carotid pulse presents variable patterns with (a) an early rise to an anacrotic notch, followed by a further delayed ascending limb, or (b) a delayed ascending limb to a delayed peak with a good amplitude of the curve, or (c) a delayed ascending limb with or without an anacrotic notch, continuing in a plateau on which vibrations may be superimposed. Patients were usually symptomatic.

In these cases the ejection angle is prolonged and the ratio E/S is equal to or greater than one. Two cases in this group came to autopsy and studies

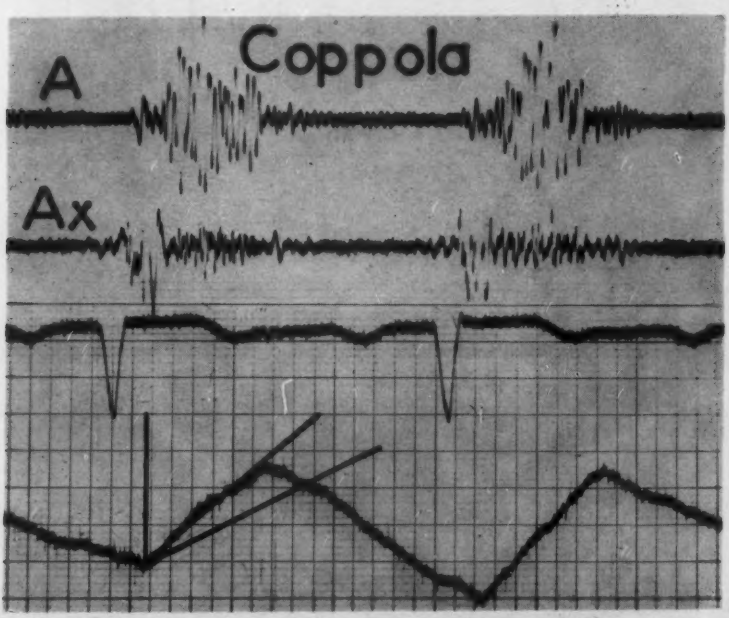

FIG. 5. Simultaneous carotid pulse curve, electrocardiogram ($_{A}V_{R}$) and stethograms from the aortic area (A) and apex (Ax). Note the loud, diamond-shaped murmur at the aortic area, which is transmitted to the apex, and the diminished second sound. The carotid pulse curve is markedly abnormal, with angle E at 50°. The incisura is barely visible. At left heart catheterization this patient had an aortic systolic gradient of 90 mm. Hg.

revealed calcareous aortic stenosis (figure 7), with an aortic opening of about 0.40 cm.^{2} in one. The other case had an aortic orifice of 0.39 cm.^{2} but with much less calcification.

3. *Nonhemodynamic Aortic Stenosis:* We include in this group patients who have clinical evidence of aortic stenosis such as a diamond-shaped murmur, a diminished or normal aortic component of the second sound, calcification of the aortic valve, and left ventricular hypertrophy by electrocardiogram or x-ray. Generally these patients were in the older age groups, with coronary artery disease, and their symptoms were difficult to evaluate. These patients have a fairly normal carotid pulse curve (figure 8),

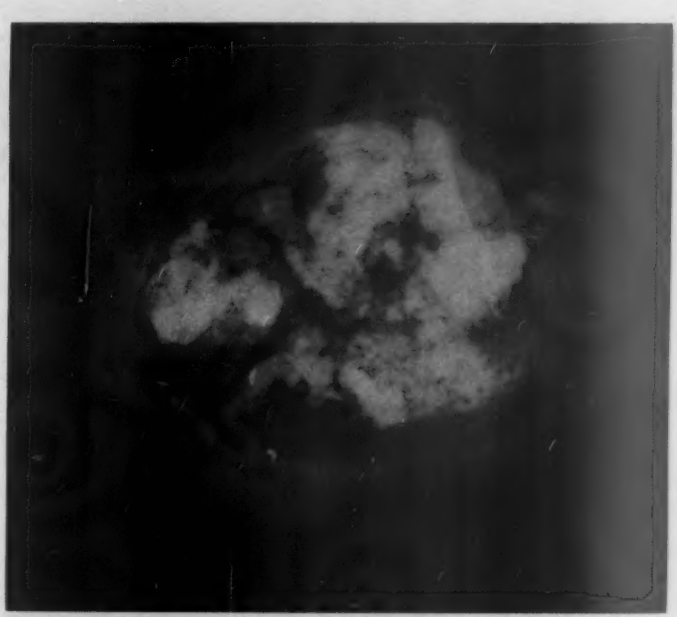

FIG. 6. X-ray of the aortic valve ring from postmortem specimen of patient in figure 5. Note the extreme calcification. The aortic orifice was almost nonexistent.

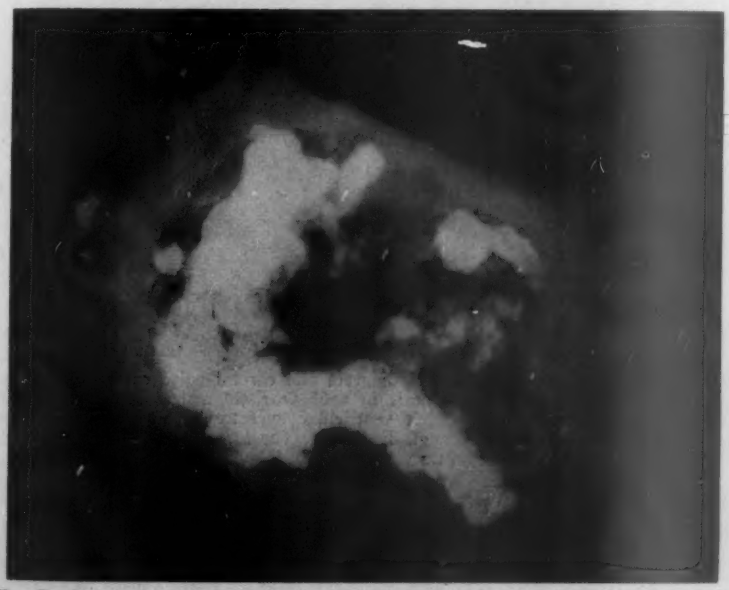

FIG. 7. X-ray of another postmortem specimen of the aortic valve ring, showing heavy calcification. Here one can see the opening of the orifice, which measured approximately 0.40 cm^2. The carotid neck cuff pulse curve was typical of aortic stenosis in this case.

but we feel that they have some degree of aortic stenosis which is not hemodynamically significant. Recent catheterization studies [81] in a somewhat similar group did not reveal any significant aortic gradient.

In combined lesions of calcareous aortic stenosis and mitral stenosis, the carotid pulse curve presents the features of aortic stenosis (figure 9).

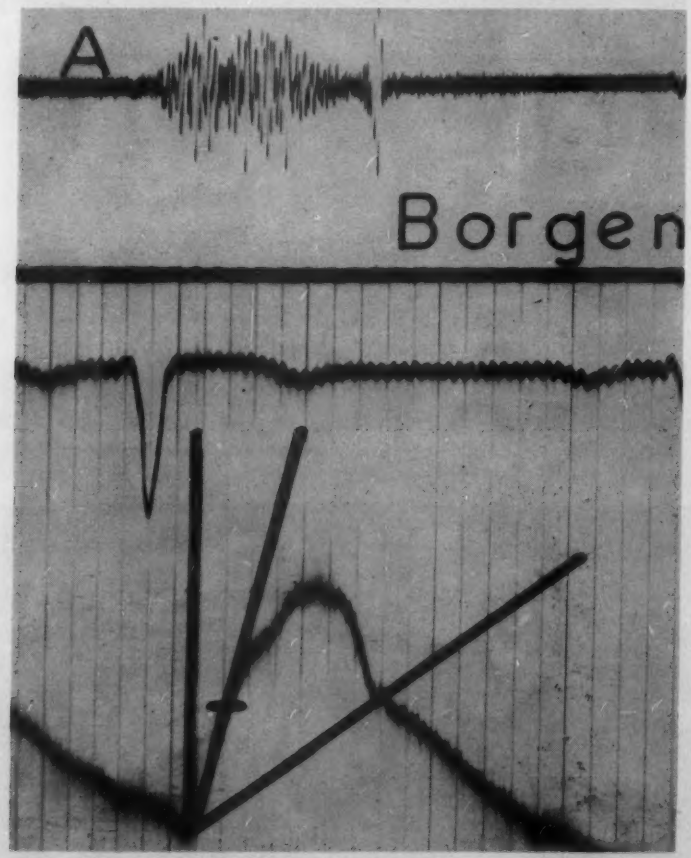

FIG. 8. Aortic stethogram, electrocardiogram and carotid pulse curve from a case of nonhemodynamic calcareous aortic stenosis in a 65 year old male. Calcium was seen in the region of the aortic valve, and left ventricular hypertrophy was present. Note the normal carotid pulse curve, with an angle E of 13°. The second sound is of good intensity and the incisura is sharp, so that aortic valve mobility is evidently present.

This patient had the typical auscultatory findings of mitral stenosis, including an opening snap of the mitral valve. A diamond-shaped murmur was present at the aortic area, and this appeared to be transmitted to the apex. Calcium was seen in the areas of both the mitral and the aortic valves. Left ventricular hypertrophy was present in the electrocardiogram and x-ray.

The carotid pulse curve confirmed the clinical diagnosis of calcareous aortic stenosis, and also led us to feel that this lesion was hemodynamically significant.

The carotid pulse curve is probably more interesting and helpful in cases where the mitral stenosis appears to be the predominant lesion. One such

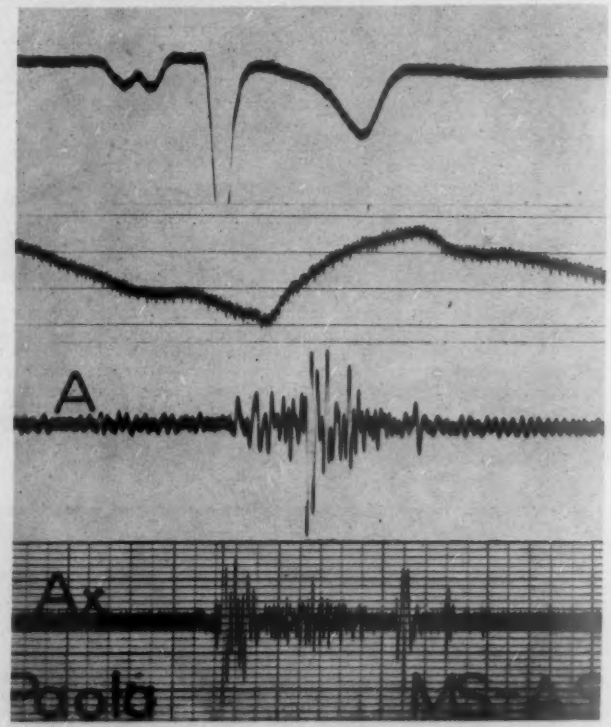

FIG. 9. Electrocardiogram, carotid pulse curve and stethograms from the aortic area and apex in a 30 year old patient with calcareous aortic stenosis and mitral stenosis. While the various angles and measurements have not been indicated on the carotid curve, the upstroke is visibly delayed and the incisura is not sharp. Angle E was 40°, and the systolic upstroke time was delayed to 0.28 second. The aortic stethogram reveals a diamond-shaped systolic murmur and a diminished second sound, which is probably the aortic component of the second sound. At the apex, note the systolic murmur which appears to be the transmitted aortic murmur, and a second sound which is probably the pulmonic component of the second sound, and, following this, an opening snap of the mitral valve. A rumbling diastolic murmur was present also but does not show in this stethogram.

patient had a complete study and was considered to have a tight mitral stenosis. A faint systolic murmur was also heard but was thought to be insignificant. The carotid pulse curve (figure 10) revealed a form suggestive of hemodynamic aortic stenosis, but this was disregarded. Mitral commissurotomy was performed, following which the patient developed heart

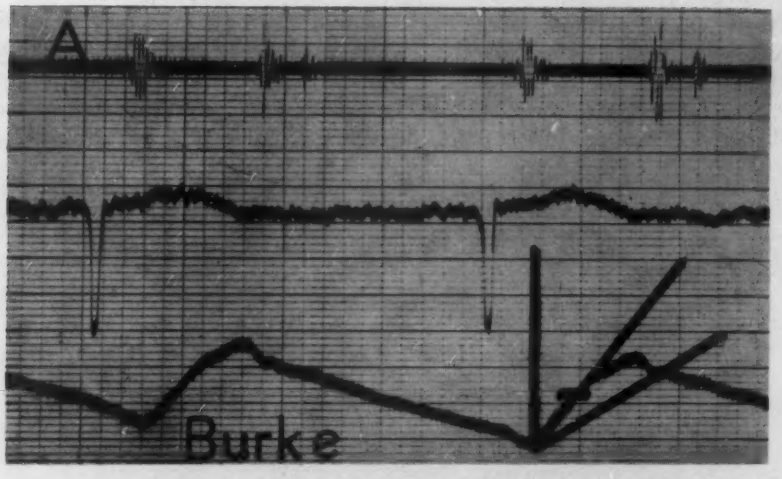

FIG. 10. A 40 year old female with mitral stenosis and calcareous aortic stenosis. Note the abnormal carotid pulse curve and the absence of any definite systolic murmur at the aortic area, although an opening snap can be seen. The carotid curve was disregarded in the diagnosis, and the patient was subjected to mitral valve commissurotomy. She died one week after operation of congestive heart failure, and postmortem examination revealed a successful commissurotomy, but the aortic valve showed marked fibrosis of the cusps, with fusing of the commissures and scattered areas of calcification. The aortic valve orifice measured 0.39 cm^2.

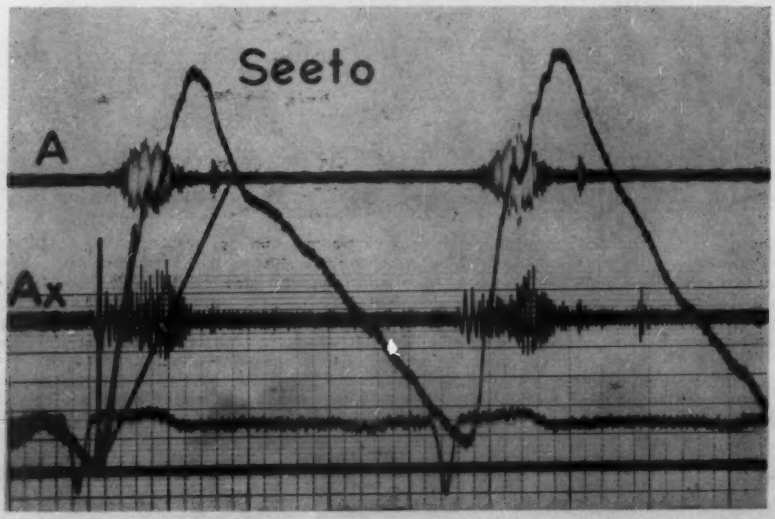

FIG. 11. A case of aortic insufficiency of syphilitic origin. Note the carotid pulse curve of the aortic insufficiency type, with a rapid rise to a high, early peak and a rapid descent with an ill-defined incisura. Note that the murmur is diamond-shaped but there was no evidence of aortic stenosis.

failure and died one week later. Postmortem studies revealed a technically successful commissurotomy but also showed aortic stenosis, with an aortic orifice measuring 0.39 cm.[2] The aortic valve showed fibrosis and fusing of the commissures. Scattered areas of calcification were seen by x-ray examination of the valve. In this case the carotid pulse curve of an aortic stenotic type should have aroused more suspicion, and we mention this case because it presents probably the ideal situation at the present time for combined surgery on the mitral and aortic valve.[40]

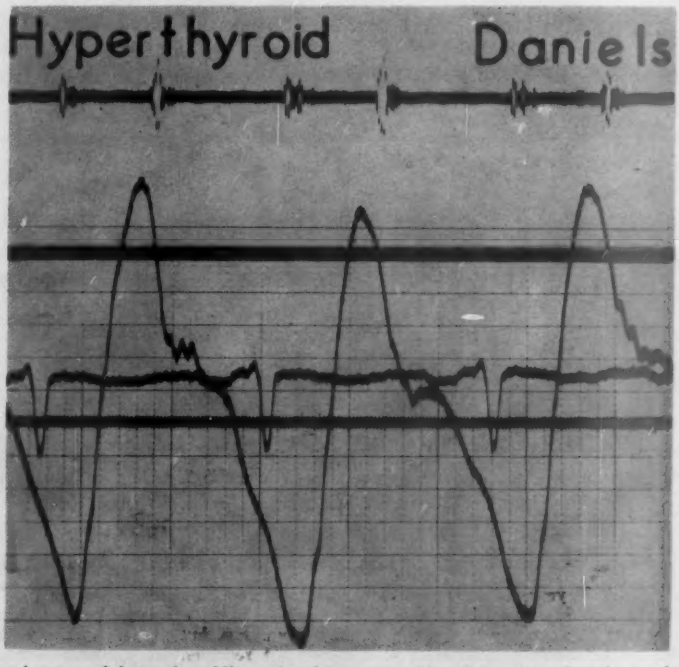

FIG. 12. A case of hyperthyroidism showing a carotid pulse wave of a form similar to aortic insufficiency, although the incisura is much sharper.

We have also found the carotid pulse curve useful in cases where the presence of a diamond-shaped murmur made the auscultatory findings difficult to evaluate. Two other cases of mitral stenosis with loud, almost diamond-shaped murmurs at the aortic area had perfectly normal carotid curves. Left heart pressure studies were performed at the time of operation and no aortic gradient could be demonstrated, although this does not definitely rule out some degree of aortic stenosis.

In pure aortic insufficiency the carotid curve reveals the well described pattern of an early, rapid rise to a very high peak, followed by a sudden drop, with an ill-defined dicrotic notch (figure 11). A similar pattern may be

seen in hyperthyroidism (figure 12). We have noted several cases where the clinical diagnoses based upon the intensity and configuration of a murmur were wrong, and cases that presented as aortic stenosis were found to have an aortic curve of aortic insufficiency, and vice versa.

In hemodynamically significant aortic stenosis combined with aortic insufficiency, the carotid neck cuff presents the features of aortic stenosis. One case of this type died, and postmortem examination revealed a rigid, heavily calcified valve with an aortic opening of about 0.40 cm^2. In other

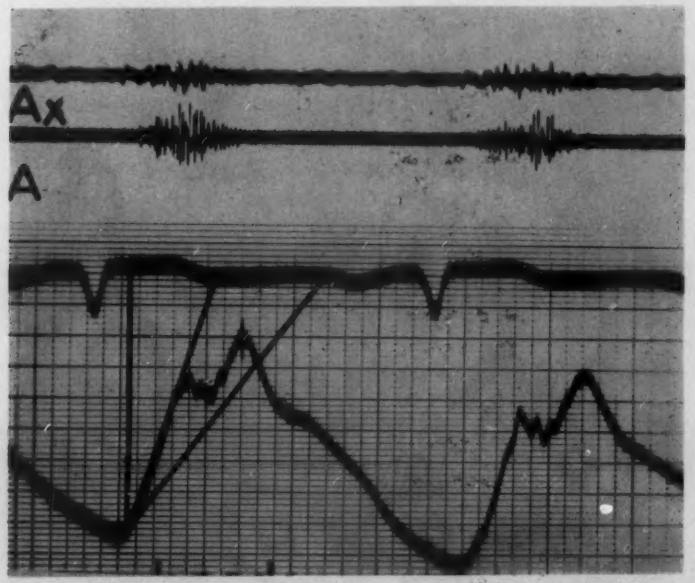

FIG. 13. A 36 year old male with aortic stenosis and insufficiency. Note that the systolic upstroke time is delayed but the angle E is within normal limits. Left heart catheterization revealed an aortic systolic gradient of 90 mm. Hg, but at postmortem examination the aortic orifice measured 1.02 $cm.^2$, which does not represent very severe stenosis. The aortic insufficiency was probably more significant hemodynamically. This illustrates the difficulty of measuring the aortic pressure gradient accurately in the presence of aortic insufficiency; under these circumstances, the form of the carotid pulse wave may be helpful.

cases the presence of aortic insufficiency may produce a carotid pulse which is far from an aortic insufficiency type but yet not conclusive of aortic stenosis. One case of this type with a carotid curve (figure 13) showing an ejection angle E of only 20° came to autopsy and showed a rigid, heavily calcified valve with an orifice of 1.02 cm^2. The patient had had previous left heart catheterization which revealed an aortic gradient of 90 mm. Hg. This is an example of the difficulty in accurate measurement of aortic gradients by left heart catheterization, particularly in the presence of aortic insufficiency.

Discussion

Our technic of obtaining the carotid pulse is open to criticism, and we recognize that the amplitude of the curve is dependent upon the amplification factor of the carrier wave amplifier, although we had worked at a constant high level of amplification. This has been the reason for measuring the angles E and S and using the ratio of E/S, since with changes in amplitude the change in this ratio is less marked. This angle E is essentially the "t" time of Duchosal, and we do not feel that measurement of the angles is necessarily superior, but we find it easier to perform, and more accurate in some cases where the anacrotic notch is early on the upstroke (figure 4).

We do not feel that the diagnosis of aortic stenosis can be established from the carotid pulse curve except in the most advanced cases, but we have found that a study of the form of this wave, when correlated with the history and the physical and laboratory findings, has been most helpful in solving some of the problems associated with the diagnosis and grading of aortic stenosis, either as an isolated lesion or when combined with other lesions.

Summary

The salient features in the diagnosis of calcareous aortic stenosis have been reviewed and a new method for obtaining the carotid pulse curve has been described. This method utilizes equipment which is commonly available in catheterization laboratories; it is simple to perform, and easy to reproduce.

An analysis has been made of the carotid pulse wave obtained by this technic in 25 normal subjects of variable age, 150 patients presenting variable cardiovascular pathology excluding aortic stenosis, and 40 patients considered to have variable degrees of calcareous aortic stenosis. Eight of the last group had proof of the diagnosis by left heart catheterization or postmortem examination.

In the presence of calcareous aortic stenosis the carotid artery pulse shows the following features: (1) delayed upstroke, revealed by an ejection angle E of more than 25° and usually more than 30°; (2) a ratio of angle E/angle S greater than one; (3) diminished to absent incisura; (4) a low pulse pressure; (5) delayed systolic upstroke time.

The routine recording of the carotid pulse simultaneously with the stethogram and electrocardiogram has been of great help: (1) in confirming an evident clinical diagnosis of calcareous aortic stenosis; (2) in suspecting aortic stenosis when features are atypical, or in the presence of other valvular lesions such as mitral stenosis and/or aortic insufficiency; (3) in attempting to grade the severity of the aortic stenosis; (4) in evaluating auscultatory findings of loud systolic murmurs with midsystolic accentuation.

We do not consider the carotid pulse curve to be a diagnostic entity in itself except in very severe calcareous aortic stenosis. It has, however,

been of great value in the proper evaluation of individual cases when used as an adjunct to the history, physical findings and other laboratory procedures.

Summario in Interlingua

Es presentate un summario del etiologia e del tableau clinic de calcari stenosis aortic insimul con un revista del acceptate constatationes laboratorial.

A parte le usual technicas laboratorial, nos ha utilisate registrationes del curva del pulso carotidic obtenite ab un simple manchette collar que es attachate a un tensiometro transductor, un amplificator de fortia appropriate, e un registrator photographic. Iste methodo es rapide, simple, e reproducibile. Esseva constatate que le curva del pulso carotidic de 25 subjectos normal e de 150 patientes con varie typos de morbo cardiovascular altere que stenosis aortic habeva (1) un ascendita rapide, (2) un inconstante indentation anacrotic, (3) un variabile plateau, (4) un acute incisura, e (5) un normal tempore de ascendita systolic, un angulo de ejection E de minus que 25°, e un proportion de angulo de ejection E a angulo systolic S amontante a minus que un.

Le angulo de ejection E es le angulo formate per le perpendiculo al initio del ascendita systolic con le tangente initial de ille ascendita. Le angulo systolic S es le angulo formate per le tangente justo mentionate e le linea connectente le initio del ascendita systolic con le incisura.

In hemodynamic stenosis aortic nos notava un lente ascendita, un micre (o absente) incisura, un reducite altor general del curva, un retardate tempore de ascendita systolic, e un angulo de ejection E de plus que 25° con un proportion de angulo de ejection E a angulo systolic S amontante a plus que 1.

Le curva del pulso carotidic se ha provate utile in casos in que le characteristicas de stenosis aortic es silente o obscurate per le presentia de un associate lesion valvular. In casos in que le diagnose esseva satis evidente, le curva del pulso carotidic se ha provate de valor confirmatori e capace a suggerer le grado de severitate del condition. Illo es possibilemente etiam de valor in stenosis aortic associate con insufficientia aortic como adjuta in evalutar le lesion predominante.

Tamen, le curva del pulso carotidic non es per se un entitate diagnostic sed un indicator adjuvante in le diagnose e le evalutation de casos de stenosis aortic.

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TREATMENT OF SCLERODERMA *

By CHRIS J. D. ZARAFONETIS, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

SCLERODERMA, or diffuse systemic sclerosis, is a challenging disease. Its etiology is not known and its pathogenesis is poorly understood. The clinical and histopathologic features of scleroderma, however, have been repeatedly described [1, 2, 3] and need be mentioned only briefly here. Characteristically there is cutaneous involvement, usually ushered in by an acute edematous phase, followed by induration and then atrophy. Raynaud's phenomenon may precede, accompany or, rarely, follow the onset of objective skin change. Pain and stiffness of joints, and myalgias are not uncommon. Although the changes in the skin may dominate the clinical picture, it is now well known that no system is immune. Diffuse sclerosis may proceed throughout the body wherever there is tissue of mesenchymal origin. Thus, changes may be induced not only in subcutaneous structures but also in the various muscles, the blood vessel walls, the esophagus and gastrointestinal tract, the lungs, heart and kidneys. Much of the involvement of the organs is manifested by fibrotic changes in the smooth muscle coats, for example, in the muscularis interna of the esophagus and bowel, or about arterioles. Signs of nonsuppurative inflammation are often found in addition to sclerotic changes.

Such profound structural alterations in tissue inevitably give rise to disturbances in function of the organs, and often to severe contractures of involved joints. Fibrotic tissue, by its very nature, undergoes shortening and thereby causes progression of contraction deformities and of atrophic changes.

In view of the type and extent of involvement, therefore, it is not surprising that fully developed scleroderma causes profound disability and is associated with a high fatality rate. Treatment has necessarily been empiric, and many and varied forms of therapy have been advocated. None has been uniformly successful and satisfactory. Nevertheless, it is believed that much can be accomplished if antifibrosis therapy is instituted early and available measures to prevent disabling contractures are fully utilized. The therapeutic program to be described is directed toward these ends. It has evolved from experience accumulated during the last decade [4, 5, 6] in the direct management of 72 cases of scleroderma, together with information concerning 10 other patients treated in a similar manner. There was no selection of

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From the Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania.

Requests for reprints should be addressed to Chris J. D. Zarafonetis, M.D., Professor of Clinical and Research Medicine, Temple University Medical Center, Philadelphia 40, Pennsylvania.

patients admitted to this series, each being placed on the program regardless of the severity of the disease. Some had previously undergone cervical sympathectomy, whereas others had been treated with corticosteroids, ACTH, testosterone, Bistrimate and other substances, without evident benefit. There were 14 males and 58 females in this series, ranging in age from three and one third to 75 years at the time of institution of therapy. The earliest onset was at the age of 10 months, in a female child who also exhibited phenylpyruvic oligophrenia.

The program followed in the management of the patients in this series consisted of (1) systemic antifibrosis therapy through the long-term administration of potassium para-aminobenzoate; (2) physiotherapy, including dynamic traction splints where applicable, and (3) Urecholine for the alleviation of dysphagia.

1. *Systemic Antifibrosis Therapy:* Some 10 years ago potassium para-aminobenzoate (Potaba, KPAB) was first observed to soften and reverse in varying degree the cutaneous changes of scleroderma.[5] At that time, large doses of the drug were administered to a 40 year old man who exhibited features of both dermatomyositis and scleroderma. Striking improvement occurred in both components of his illness, and this led to the further use of Potaba in the treatment of scleroderma.

For administration to patients, potassium para-aminobenzoate has been found to be preferable to the crystalline acid or the sodium salt. The potassium salt is less frequently associated with anorexia and nausea. Like other potassium compounds, however, KPAB is best given in liquid form. Patients generally prefer a chilled 10% aqueous solution of KPAB to other preparations. Capsules are often well tolerated, but tablets not infrequently cause abdominal cramps.

Since KPAB is rapidly excreted in the urine, it is necessary to administer repeated doses at approximately three-hour intervals to maintain optimal therapeutic effectiveness. Adults with scleroderma are usually given 12 gm. daily, divided into six doses of 2 gm. each. Thus, the patients take 20 c.c. of the 10% solution, or 2 gm. in capsules, six times a day. Children who weigh less than 100 pounds are given 1 gm. per 10 pounds of body weight daily, with the total for each day divided into six equal doses. It is usually convenient to schedule doses at breakfast, midmorning, lunch, midafternoon, dinner and bedtime. Most of the patients adjust to this schedule readily when its purpose is explained to them. Should anorexia or nausea occur, therapy is interrupted until the patient is again eating well. By interrupting therapy, one not only permits the prompt subsidence of symptoms but also prevents the development of hypoglycemia. The latter may occur if the administration of KPAB is continued through a period of inadequate food intake.

Aside from an adequate dosage schedule, the most important requirement of Potaba therapy is that of prolonged administration. This is evident in

the illustrative case reports presented below, and is strikingly demonstrated in table 1, which summarizes the over-all results obtained in this series. Of the subjects who were treated for more than three months, only two of 60 failed to show moderate to marked cutaneous improvement. The skin gradually softens, becomes loosened from and freely movable over subcutaneous structures, and is wrinkled with increasing ease. Gain in weight and subjective improvement generally accompany the improvement in skin texture.

TABLE 1

Duration of Therapy with Potaba Related to Skin Improvement at Time of Evaluation of 72 Cases of Scleroderma

Skin Improvement	Period of Treatment		Total
	Less Than 3 Months	More Than 3 Months	
None to slight	5*	2†	7
Moderate	5	34‡	39
Marked	2	24	26
Total	12	60§	72‖

* One patient died of acute cardiac insufficiency early in course of treatment.

† In one subject, weight loss continued while on KPAB therapy; treatment was changed to cortisone without benefit, and he later succumbed.

‡ Addition of Meticorten, 5 mg. every eight hours, to therapeutic program of one patient was followed by development of hypertension, cardiac failure, "scleroderma kidney" and death.

§ Four patients died of cancer while under treatment.

‖ Personal communications dealing with 10 additional cases of scleroderma treated with Potaba indicate moderate to marked improvement in nine, and no noticeable improvement in one subject who received medication for only three months.

CASE REPORTS

Case 1. An iron foundry worker had been in good health until 1948 when, at age 62, he developed generalized scleroderma. His disease progressed gradually, with loss of 25 pounds in weight, muscle weakness and easy fatigability. Raynaud's phenomena of the hands and feet were noted, and he complained of difficulty in swallowing solid foods. Varied forms of therapy did not arrest the progress of his disease.

The patient was first seen at the Temple University Hospital on March 19, 1951. By this time he was very weak and used a cane to get about. Typical findings of scleroderma were present, including flexion deformities of most joints. His skin was stiff and bound to underlying structures. There was some hyperpigmentation. Roentgenographic studies disclosed pulmonary fibrosis and associated emphysema, and esophageal changes were also detected.

Potassium para-aminobenzoate therapy was begun on May 15, 1951 (figure 1A), and has been continued to date. There was slow but steady improvement in the texture of his skin, as can be seen in the photograph taken after four months of treatment (figure 1B). In addition to the cutaneous improvement there was gradual gain in weight, strength and mobility, and the patient discarded his cane. Dysphagia was no longer experienced. He has remained on Potaba and physiotherapy to the present time because there is roentgenographic evidence that he still has pulmonary

FIG. 1.

FIG. 2A. Right hand of case 1 on January 30, 1958. Note looseness and pliability of skin. B. Same hand as in figure 2A, January 30, 1958. Despite marked improvement of skin and hand function, residual pericapsular contracture still prevents full flexion of fingers.

fibrosis (to which his occupation may have contributed) and because he has some residual limitation of joint function (figures 2A and 2B). His appearance on January 30, 1958, is shown in figure 1C.

Comment: This patient has taken Potaba, 12 gm. daily, for seven years without difficulty. He has also carried out prescribed exercises to aid in regaining joint mobility. His clinical response has been highly gratifying.

Case 2. A white male iron molder first had manifestations of scleroderma in 1949, when he was 49 years old. His disease was generalized, and slowly progressed.

FIG. 1A. Base line photograph of case 1 on May 15, 1951, just before institution of Potaba therapy. Note that skin is thickened and bound to subcutaneous tissues. This is maximal abduction of the shoulders. B. Case 1 as he appeared on September 6, 1951, after four months of therapy. Note increased pliability of skin, gain in weight, and greater elevation of the arms. C. Case 1 photographed on January 30, 1958, after more than six years of treatment. Note sustained improvement.

In October, 1950, ACTH was administered twice daily for 30 days for treatment of his "arthritis." He felt improved while receiving therapy, but he relapsed promptly after the ACTH was discontinued. He was then placed on oral cortisone, beginning at 200 mg. daily, with gradual reduction of dose over a two-month period. Again relapse ensued and he was unable to arise from his bed. In February, 1951, a biopsy

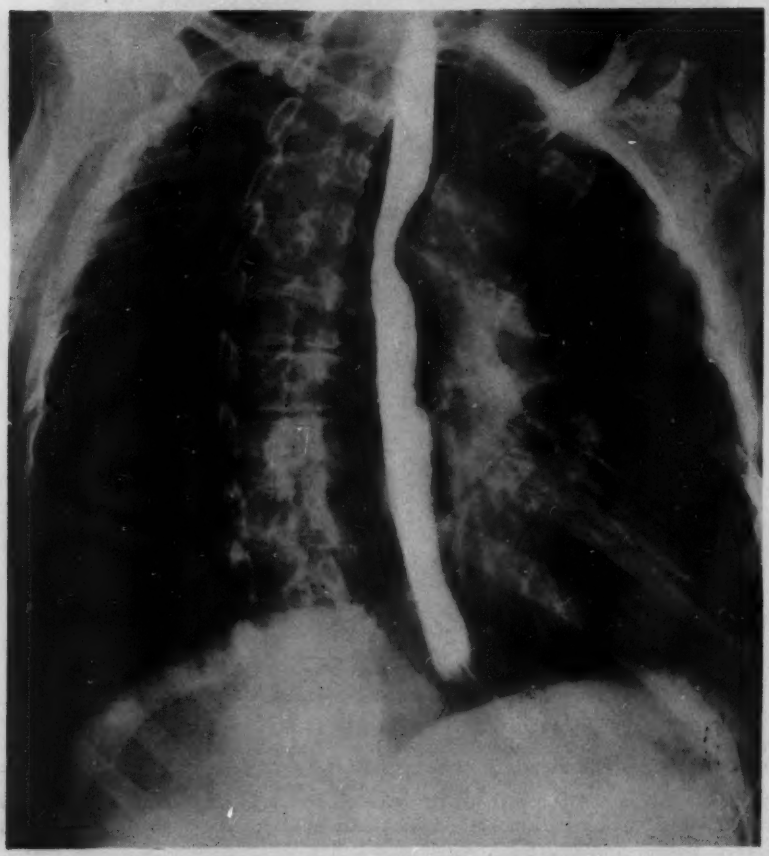

FIG. 3. Roentgenogram taken during esophageal study of case 2 on July 8, 1953. Fluoroscopic examination revealed feeble and ineffective peristalsis, with delayed transport of the barium column.

of the skin was taken and showed the typical changes of scleroderma (figure 5A). Testosterone injections and a course of intravenous ACTH therapy were also without sustained effect, as was vitamin E concentrate.

By September, 1951, the patient was very uncomfortable. Skin involvement was generalized. His arms and legs ached a great deal, especially at night. Most of his joints were painful, and he had difficulty in arising after sitting in a chair. Nausea, dysphagia and esophagitis were troublesome symptoms. He also complained of a dry, hacking cough. Treatment with KPAB, 12 gm. daily, was begun on Sep-

tember 24, 1951. In addition, aspirin, 0.5 gm. four times daily, was prescribed for pain. His response to treatment was gradual, but definite improvement was evident within two months. As joint and muscle pain subsided he was encouraged to perform range-of-motion exercises for his various involved joints. He gained 28 pounds in weight during the first 10 months of treatment. The gain in weight continued during the following year, after which his diet was restricted. There was steady improvement in texture of the skin and of strength and mobility. He still had esophageal distress, however, and cough was also troublesome. Roentgen studies showed abnormal function of the esophagus (figure 3).

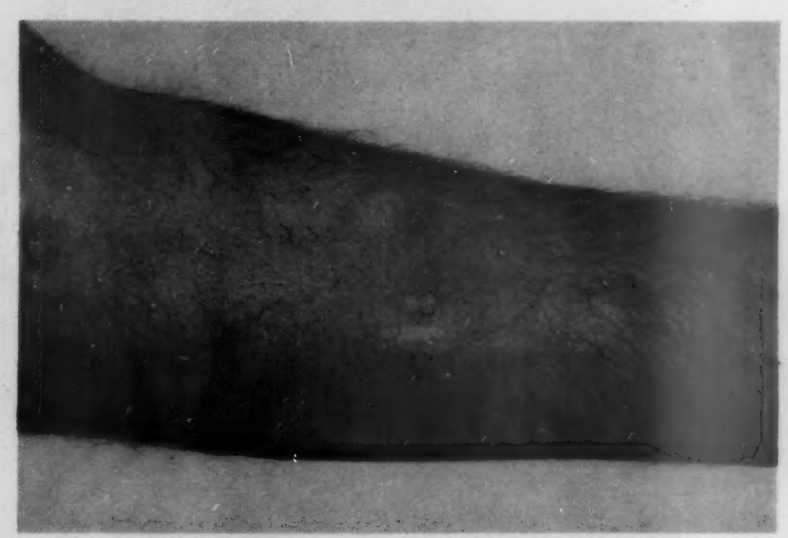

FIG. 4. Arm of case 2 photographed on December 1, 1955, to show sites of skin biopsies. Scar above represents site of specimen taken in August, 1955 (figure 5B), and the lower scar was made in taking the first biopsy, February, 1951 (figure 5A).

Potaba therapy has been maintained to the present time. The skin improvement has been excellent (figures 4 and 5B). There is no serious joint difficulty, although some limitation of digital flexion persists, due to pericapsular contraction. Esophageal distress is now only occasionally noted and is controlled with Urecholine. The patient's principal complaints are cough and attacks of dyspnea. So far, studies have failed to provide an explanation of these symptoms.

Comment: Treatment of this patient elsewhere with ACTH, cortisone and other measures was unsuccessful. His response to Potaba and salicylates was gradual but progressive. Skin texture, weight, strength, and muscle and joint function are now normal or very nearly so. Dysphagia was a problem until Urecholine was added to his program.

2. *Management of the Consequences of Pericapsular Fibrosis:*

a. *Physiotherapy and dynamic traction splints:* Early in the course of these studies it was observed that, despite cutaneous improvement, there was often no significant improvement in the range of motion of involved joints.

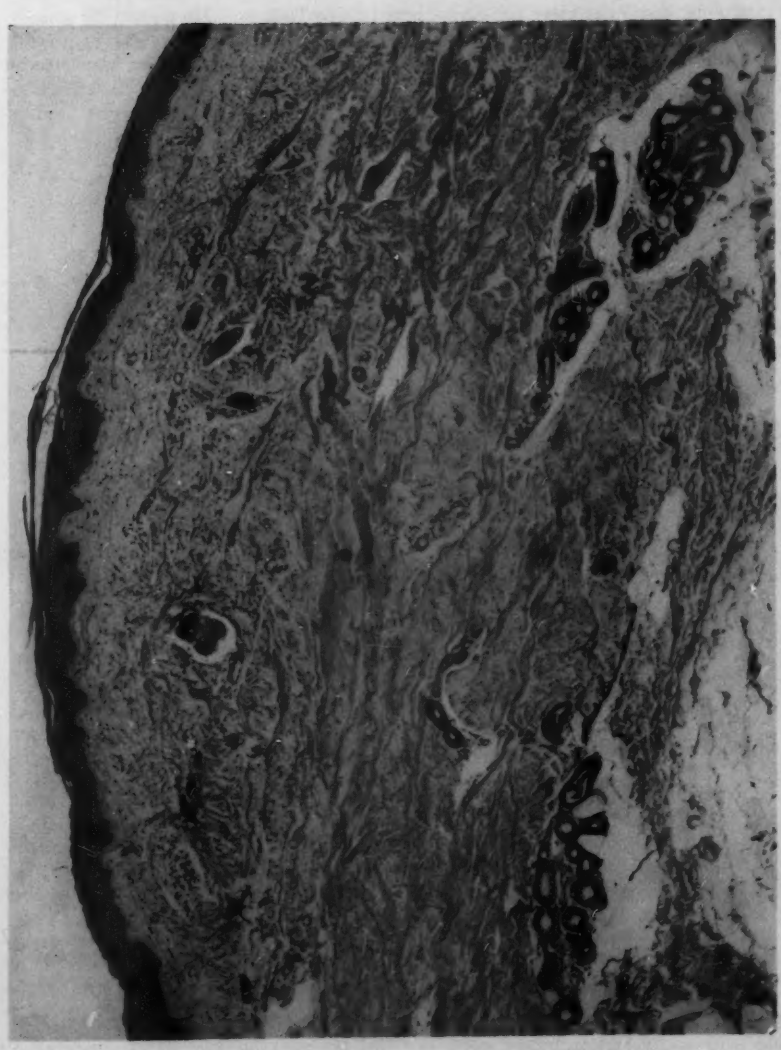

FIG. 5A. Section of skin biopsy taken from arm of case 2 in February, 1951. Magnification × 60. Typical findings associated with scleroderma are seen.

FIG. 5B. Section of skin biopsy taken from arm of case 2 in August, 1955, after four years of therapy. Same magnification as in figure 5A. Note that histologic features are not dissimilar, but the thickness from surface to subcutaneous fat is much reduced in the post-treatment specimen.

Roentgenographic studies generally revealed no intra-articular changes to account for persistence of the contractures. It was then recognized that pericapsular involvement was part of the disease process. The observed contractures were therefore consequent to pericapsular fibrosis.[6] Because of myositis, myalgia and arthralgia, scleroderma patients tend to favor their joints. The less joints are mobilized, the more the contractures that follow. Involvement of the overlying skin further aggravates the patient's difficulties. Progressive disability results. Although contractures of finger joints are often prominent, the wrists, elbows, shoulders, jaw and joints of the lower extremities are also often involved.

FIG. 6A. Appearance of hands of case 3 on December 27, 1949, prior to institution of therapy. Note inability to press hands flat on table, and firmness of tissues of forearm.

It is therefore advisable to institute physiotherapeutic measures in addition to Potaba therapy as early as possible. Active and passive physiotherapy, including range-of-motion exercises, should be a regular feature of the therapeutic program. Dynamic traction splints may be particularly valuable in restoring function of the hand. These may be constructed to aid in overcoming limitation of either flexion or extension of the fingers. It should be evident that the value of such splints is directly proportional to the amount of time they are worn each day. Patients need to understand that a few minutes' use of a splint cannot overcome the contractive forces which are unopposed for the remainder of the day.

The following case report exemplifies the result which can be achieved when these principles of therapy are adhered to.

Case 3. A 37 year old white female was referred to the University Hospital at Ann Arbor, Michigan, on December 27, 1949, for treatment of scleroderma. She had experienced an abrupt onset of the edematous phase of scleroderma on August 6, 1949. The swelling of the hands, arms and legs was particularly marked, so that there was dimpling at the involved joints. The edema gradually subsided, leaving the skin firm and bound to the subcutaneous structures. Contractures of the fingers

FIG. 6B. Photograph of case 3 taken in April, 1958. Note complete extension of fingers and ready wrinkling of skin of forearm.

ensued. The calf muscles and Achilles tendons were also shortened, so that she could not stand with her feet flat on the floor. An irregular low grade fever had been noted, with considerable loss of weight since the onset of illness.

Examination revealed, in addition to the above findings, a puffiness about the eyes. There was absence of hair on the arms and legs. An oval, morphea-type lesion 5 by 10 cm. on the back had been present for approximately 20 years.

Base line photographs were taken (figure 6A), and therapy with KPAB, 12 gm. daily, was begun on December 28, 1949. Treatment was well tolerated, and four weeks later, despite the loss of the edema which had been present in the patient's face and ankles, she had gained six pounds in weight. There was little perceptible

change in skin texture. However, physical activity had been increased, and the patient volunteered that she could now shake down a thermometer and use a can-opener.

After an additional four weeks of KPAB the involved skin was definitely softer

Fig. 7A. Voluntary extension of right hand of case 3 was still limited after five months of KPAB therapy (May, 1950). B. Dynamic traction splint built for use of case 3 (May, 1950). C. View of same hand in April, 1958, shows excellent end result of treatment.

and there was considerable increase in range of motion of the fingers, wrists and ankles. The muscles of the forearms had also softened somewhat. The patient was now well enough to resume her occupation.

Progressive improvement continued, but despite softening of the skin, limitation of extension of the fingers remained, especially of the right hand. This was attributed to shortening of the pericapsular fibrous tissues. For this reason a dynamic traction splint was constructed for the right hand and its use added to the therapeutic program (figures 7A, 7B and 7C). Beginning on May 27, 1950, the splint was worn for a few minutes several times daily. It was painful at first, but the patient was able to wear it for progressively longer intervals. After about a month the splint was worn almost continually during the day. By October, 1950, the fingers were essentially straight and use of the splint was discontinued.

Treatment with KPAB, 12 gm. daily, was not stopped until July, 1951, however, at which time it was interrupted for two weeks, then resumed at 8 to 10 gm. daily until April, 1952. The dosage was then gradually reduced and the drug was discontinued on May 30, 1952, after almost 18 months of therapy.

The patient's scleroderma has since been in remission. Aside from improvement in the texture of the skin, and function of the joints and muscles, the patient regained and maintained her normal weight. It is of interest that only slight hyperpigmentation remains in the site of the morphea-like area. When last seen, in April, 1958, the patient was well and showed no evidence of reactivation of the disease process. Skin texture was excellent (figure 6B), and she had complete functional use of her hands (figure 7C).

Comment: This patient is remarkable for several reasons. Her case is a rare, if not unique, instance of scleroderma occurring in an individual who had developed an area of morphea some 20 years earlier. Second, the almost complete remission of the disease process which was achieved through KPAB therapy has persisted for more than six years, to date. Finally, her intelligent use of a dynamic traction splint aided in the restoration of a normal range of motion for the joints of the right hand.

b. *Deep-breathing exercises:* Low vital capacity is commonly found in subjects with generalized sclerosis, even in the absence of pulmonary edema. Pulmonary fibrosis, pleural adhesions and involvement of the skin of the chest wall have all been implicated as contributing factors. Although Potaba therapy is generally followed by progressive softening of the skin over the thorax as well as elsewhere, we were impressed by the fact that relative rigidity of the thoracic cage often persisted. Indeed, maximal expansion of the chest in some of these patients has been as little as 1.5 cm. We therefore suspected that the costovertebral and the costosternal joints had experienced pericapsular fibrosis and contracture in a manner similar to that already noted for joints of the hands. The following brief case summary will serve to illustrate this and several other interesting aspects of scleroderma.

Case 4. A 49 year old white saleswoman was first seen in January, 1956, for treatment of generalized scleroderma which had had its onset in 1954. She was placed on Potaba, 12 gm. daily, and range-of-motion exercises. During the ensuing 16 months there was moderate improvement of the fibrotic component of her disease, with definite loosening of the skin over the thorax. However, she continued to

complain of myositis and joint pains, which were fairly satisfactorily relieved with salicylates. Dysphagia was a prominent symptom at first, but this was ameliorated by Urecholine. The blood pressure readings were normal throughout most of her course, generally at a level of 110/60 mm. of Hg. In April, 1957, external spirometry revealed the vital capacity (standing) to be 1,050 ml., and the maximal breathing capacity to be 20 L. per minute. Maximal chest excursion was one-half inch. Accordingly, deep breathing exercises were added to her program. During the next

FIG. 8A. Kidney from case 4. Note gross hemorrhagic areas along cortical margin.

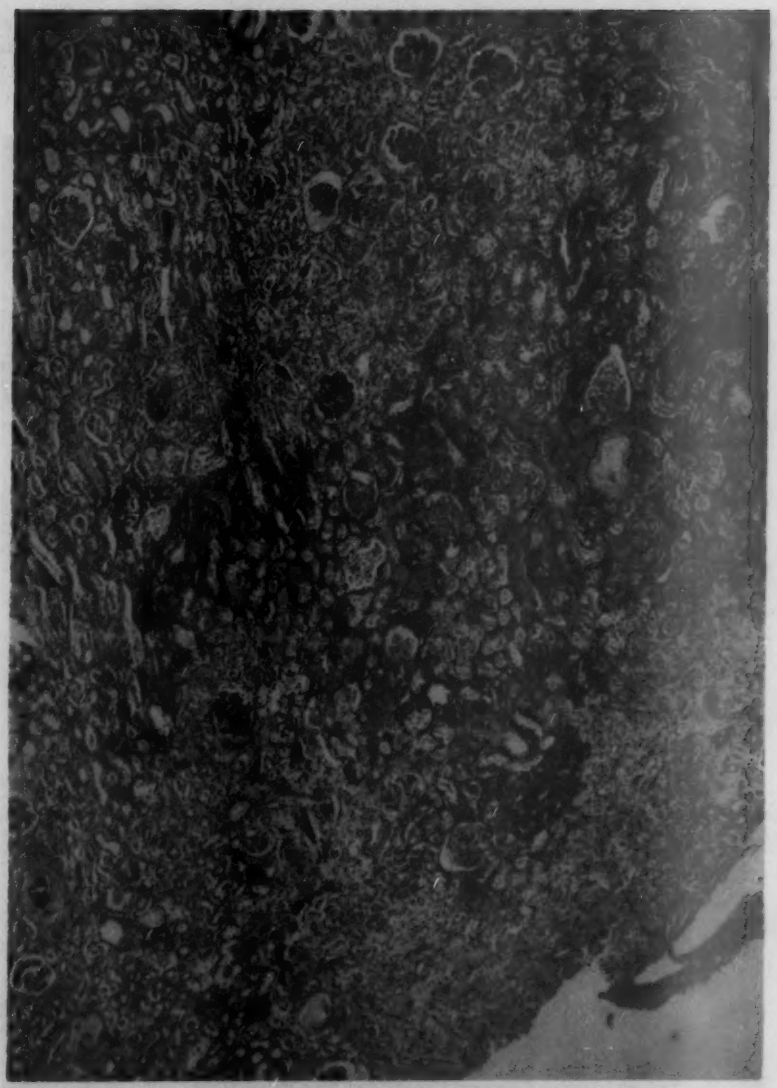

FIG. 8B. This section of kidney from case 4 shows cortical necrosis with a zone of hemorrhage separating viable (upper right) from necrotic tissue (lower left). To the right and above center of this photomicrograph is a sclerotic artery showing fibrinoid necrosis. (×44).

few months pain in the muscles was increasingly troublesome and was accompanied by progressive weakness and atrophy. At this time the patient heard that cortisone was a recommended form of therapy for her disease and demanded its use in her case. In this situation, it was explained to the patient's family that the administration of

corticosteroids to scleroderma patients carried a significant risk of hypertension and probably enhanced the incidence of "scleroderma kidney." [7] In view of the patient's psychologic state and other circumstances, it was agreed at the family's request to undertake a brief course of Meticorten therapy. This was begun with 5 mg. every

FIG. 8C. Higher magnification (× 200) of section of kidney from same patient shows fibrinoid necrosis of two previously sclerotic arteries, fibrinoid degeneration of the arteriole of one glomerulus (upper left), and fibrinoid thrombi in the capillaries of both glomeruli.

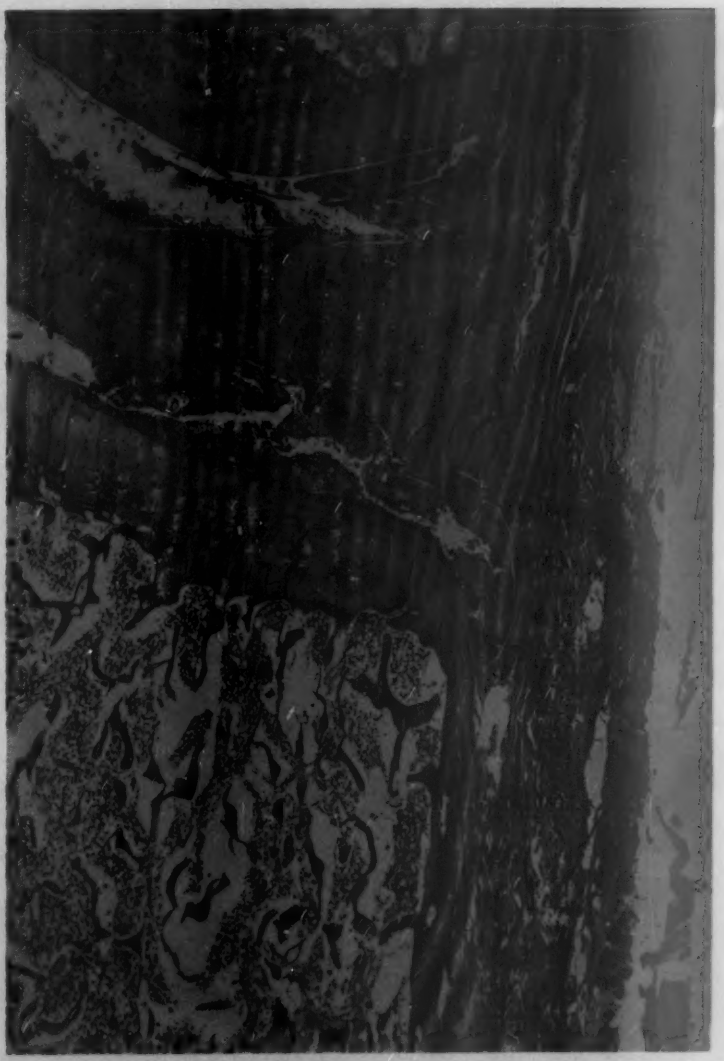

FIG. 9A. Section through costosternal articulation from case 4. This low power view (×9) shows increased pericapsular fibrous tissue (upper right and center) composed of dense, thickened collagenous-type bundles and some amorphous ground substance. This pericapsular fibrosis limits movement of the joints and thereby inhibits respiratory excursions of the thorax.

eight hours, with improvement of the muscular complaints for about two weeks. Thereafter, however, these symptoms were exacerbated, and profound weakness developed, with deep thoracic and midepigastric pain, and severe cough and dyspnea. She became bed-ridden and needed to be hospitalized. Her blood pressure had risen to 180/124 mm. of Hg, and acute pulmonary edema and gallop rhythm ensued. There

was no response to treatment, and she died six weeks after the administration of corticosteroid was begun.

Although postmortem examination revealed the widespread changes of diffuse sclerosis, mention will be made of only two findings. The acute and profound kidney lesions which were present are illustrated in figures 8A, 8B and 8C. Cortical necrosis,

FIG. 9B. Section through costovertebral articulation from case 4. Again there is a significant degree of pericapsular fibrosis. (× 15).

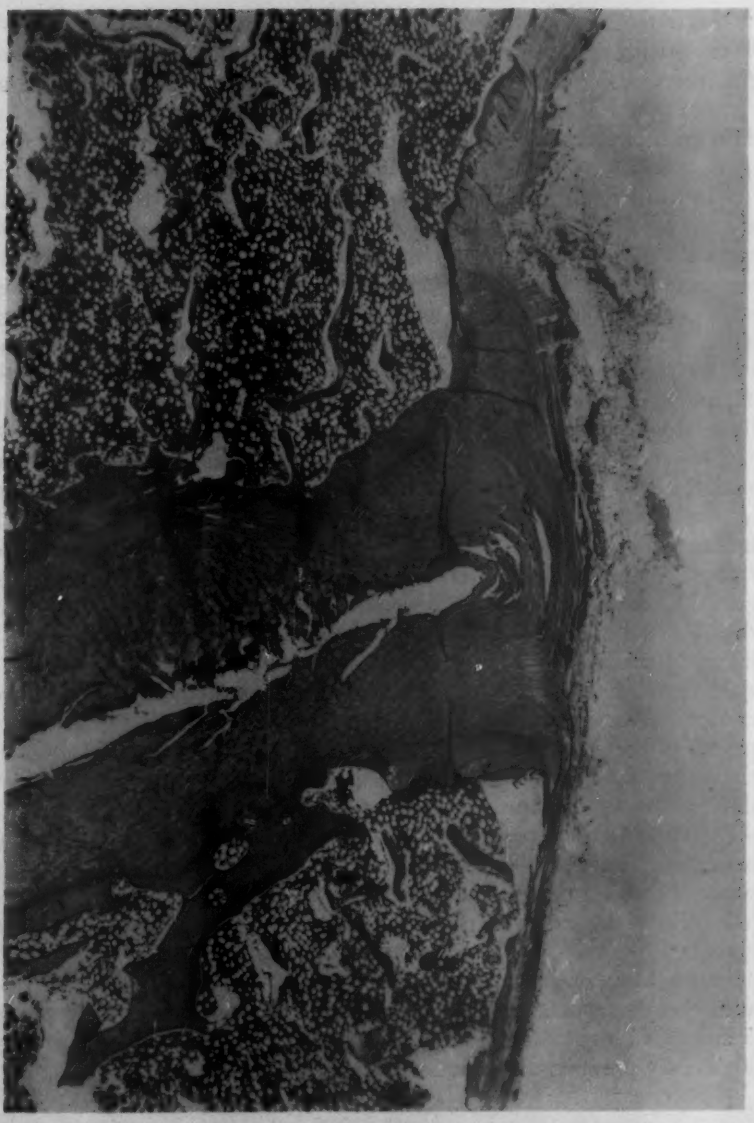

FIG. 9C. Section through a normal costovertebral articulation for comparison with 9B. Note the relatively thin fibrocollagenous capsule. (×15).

hemorrhage and glomerular involvement are well demonstrated. Figure 9A shows a section through a costosternal joint which exhibits marked increase in pericapsular fibrous tissue. Similar findings were noted in a costovertebral articulation (figure 9B), which may be compared with the relatively thin capsule of a normal costovertebral joint (figure 9C).

Comment: This patient's course illustrates several important points in connection with the treatment of scleroderma. First, it should be evident that severe cases of the disease may continue to deteriorate despite the administration of KPAB, which, however, appears to have a delaying effect even in such patients. Second, the development of hypertension and acute congestive failure, together with "scleroderma kidney," which closely followed institution of Meticorten therapy, is highly suggestive of a causal relationship. This sequence has not been observed in any of the remaining patients in this series who were treated with KPAB alone. Finally, histologic evidence obtained at necropsy strongly supports the view that pericapsular fibrosis contributes importantly to the embarrassment of ventilatory function in the scleroderma patient. For this reason, Potaba administration should be started as early as possible in the course of the disease, and deep breathing exercises should be part of the daily physiotherapeutic regimen of these individuals.

3. *Management of dysphagia:* In addition to the basic program of Potaba administration along with appropriate exercises and splints, attention should be drawn to the problem of therapy for dysphagia in scleroderma. This symptom has been recognized by numerous workers and has generally been attributed to fibrotic changes in the esophageal wall. Morphologic changes (figure 3) are undoubtedly of importance in producing symptoms. Recent studies by Lorber and Zarafonetis,[8] however, have also revealed a high incidence of functional dysphagia associated with a deranged motor pattern in subjects with scleroderma. Of 25 consecutive cases in whom esophageal transport studies were performed, dysphagia was present in 17, but normal emptying of the esophagus was observed in only two. There was absence of the primary peristaltic wave in 17 patients, and failure of the vestibule to contract was noted in four. There were 14 patients whose esophagus failed to empty within three minutes after a test swallow of barium mixture. Administration of 5 mg. Urecholine subcutaneously resulted in more rapid transport in all but one of these subjects. Injection of 25 mg. of Dibuline, on the other hand, led to esophageal retention of three minutes in 20 of the 25 patients.

On the basis of the foregoing observations, Urecholine has been prescribed for those patients with scleroderma who complain of dysphagia. A 5 mg. or 10 mg. tablet, crushed and swallowed one-half hour before each meal, usually prevents or minimizes this difficulty.

Discussion

The course of an individual patient with scleroderma may be variable and unpredictable. It is believed, however, that the cumulative experience gained with this series of 72 patients is sufficient to show a causal relationship between therapy and response. The preceding case reports, along with the data in table 1, clearly indicate that the long-term administration of

Potaba in adequate dosage will produce moderate to marked improvement in the great majority of scleroderma patients. It is recognized, however, that Potaba is not a complete treatment for scleroderma. In the highly active, rapidly progressive form of disease, Potaba may only retard the process.

Untoward reactions to KPAB have been documented elsewhere.[4, 5, 6, 9] These consist mainly of gastrointestinal complaints such as anorexia and nausea, which will subside after omission of the drug for a day or so. Treatment may be resumed as soon as the patient is eating well. By interrupting therapy during periods of poor dietary intake, one may prevent the development of hypoglycemia. Scleroderma patients with dysphagia may also occasionally note a burning sensation after swallowing a dose of the medication. This is usually relieved by antacids or milk.

These effects are not considered to be true toxic reactions. Indeed, Potaba is remarkably free from toxicity in doses employed in these and related studies. A few instances of drug rash and drug fever have been encountered, especially in lupus erythematosus patients. Leukopenia may at times be encountered during KPAB therapy, but its significance is difficult to assess, since there is often a return to normal values despite continued administration of the drug. In more than 500 patients treated in this and other studies, no agranulocytosis has been encountered.

The mechanism by which Potaba mediates its effects in scleroderma has not been elucidated. However, there have been some recent studies which appear to bear directly on this point. First, a case of functioning carcinoid syndrome was observed that also exhibited scleroderma-like features.[10] The association of these findings was interpreted as a potential clue to the pathogenesis not only of the fibrotic changes of the functioning carcinoid syndrome but also of those of scleroderma and other fibrotic states.[11] It was postulated that such fibrotic changes might result from a deranged interaction of the serotonin-mono-amine oxidase mechanisms at the tissue level. Fibrosis was believed to occur whenever an excess serotonin effect was sustained over a sufficient interval of time. This could result from either too much serotonin or too little mono-amine oxidase activity.

If this concept is correct, it may also offer a possible explanation of the mechanism by which the administration of Potaba causes regression of abnormal fibrosis. In this connection, it is known that mono-amine oxidase requires an adequate supply of oxygen to function properly. Tissue anoxia will therefore depress mono-amine oxidase activity and, according to the theory, fibrosis will tend to occur or progress. On the other hand, anything that increases oxygen at the tissue level should enhance mono-amine oxidase activity and prevent or bring about regression of fibrosis. Some time ago Greiff [12] undertook studies designed to determine the mode of action of para-aminobenzoic acid (PABA) in rickettsial infections. He demonstrated that the injection of PABA into the yolk sac markedly increased

the oxygen consumption of the developing chick embryo. He further demonstrated that this increased cellular respiration occurred even though cytochrome oxidase activity was blocked with cyanide. Since mono-amine oxidase is insensitive to cyanide, this enzyme may represent the pathway through which PABA mediates increased oxygen uptake at the tissue level.

Attention has been drawn to another major difficulty in the management of scleroderma, namely, pericapsular fibrosis and the joint contractures which ensue from this process. In addition, it has been shown that there is a similar involvement of the articulations of the thoracic cage. This may lead to rigidity of the thorax and embarrassment of ventilatory function. It is of the greatest importance, therefore, that physiotherapeutic measures, including deep breathing exercises, should be started early and maintained indefinitely in patients with scleroderma. The supplemental use of dynamic traction splints has been particularly valuable in dealing with contractures of the hands.

Many scleroderma patients complain of dysphagia and show evidence of a deranged esophageal transport mechanism. Urecholine affords relief to these individuals.

Finally, it should be recognized that a chronic disease such as scleroderma will require chronic treatment. In the absence of specific therapy for this disease, any program of management which is followed should be safe for long-term use, should be practical, and should be economically feasible. It is believed that experience with the therapeutic regimen described herein indicates that it conforms to these requirements.

ACKNOWLEDGMENT

Grateful appreciation is expressed to Dr. Harvey M. Watts for the photomicrographs used to illustrate the renal and articular findings in case 4.

SUMMARIO IN INTERLINGUA

Es presentate le resultatos obtenite in le tractamento de 72 consecutive casos de scleroderma. Le regime esseva (1) therapia anti fibrosis systemic, per le prolongate administration oral de para-amino-benzoato de kalium (Potaba) in un dosage amontante a 12 g per die, (2) physiotherapia, incluse exercitios de respiration profunde e—in tanto que applicabile—apparatos de traction dynamic, e (3) Urecholina pro le alleviation del dysphagia.

Inter le 60 subjectos qui recipeva Potaba durante plus que tres menses, solmente duo non monstrava marcate o moderate meliorationes cutanee. Administrationes prolongate del droga in doses adequate se provava indispensabile pro inducer un regression del componente fibrotic del morbo.

Fibrosis pericapsular es un parte del processo pathologic e resulta in contractura articular. Es etiam presentate datos que indica que le mesme typo de affection articular occurre in le cagia thoracic. Rigiditate del thorace pote esser un consequentia con le resultato de un serie embarasso del function ventilatori. Il es, per consequente, del plus grande importantia que mesuras physiotherapeutic, incluse exercitios de respiration profunde, es instituite promptemente e es mantenite persistentemente in omne patientes con scleroderma. Es presentate exemplos que prova que apparatos de traction dynamic es specialmente utile in le tractamento de contracturas del mano.

Es citate studios del transporto esophagee, effectuate in 25 consecutive patientes con scleroderma. Dysphagia esseva presente in 17 casos, sed un vacuation normal del esophago esseva trovate in solmente duo. Le administration subcutanee de 5 mg de Urecholina resultava in un acceleration del transporto esophagee in omne casos, con un exception. Super le base de iste constatationes, Urecholina es prescribite pro patientes de scleroderma qui se plange de dysphagia. Un tabletta de 5 o 10 mg, contundite e inglutite un medie hora ante omne repasto, se monstrava capace a prevenir o reducer le difficultate mentionate.

Il debe esser signalate emphaticamente que scleroderma es un morbo chronic que require un therapia chronic. Per consequente—e viste que il non existe un tractamento specific pro iste disordine—omne programma therapeutic que es initiate debe esser innocente in uso prolongate, e illo debe esser practic e economicamente possibile. Es opinate que le regime describite in le presente articulo satisface ille requirimentos.

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RHEUMATISM AND ARTHRITIS:

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(TWELFTH RHEUMATISM REVIEW) *

Part I

By Charley J. Smyth, M.D., F.A.C.P., *Denver, Colorado*
(Chairman, Editorial Committee),
Joseph J. Bunim, M.D., F.A.C.P., *Bethesda, Maryland,*
William S. Clark, M.D., F.A.C.P., *New York, N. Y.,*
Darrell C. Crain, M.D., F.A.C.P., *Washington, D. C.,*
Felix E. Demartini, M.D., *New York, N. Y.,*
Ivan F. Duff, M.D., F.A.C.P., *Ann Arbor, Michigan,*
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Howard F. Polley, M.D., F.A.C.P., *Rochester, Minnesota,*
Marian W. Ropes, M.D., F.A.C.P., *Boston, Massachusetts,* and
Edward F. Rosenberg, M.D., F.A.C.P., *Chicago, Illinois*

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Definition of "Rheumatism" and "Rheumatic Diseases"

As in previous reviews, these terms are used to denote a broad group of musculoskeletal disorders manifested by pain and stiffness, swelling and other

* Received for publication August 4, 1958.

The last Review prepared by the Editorial Committee of the American Rheumatism Association was the Eleventh; it concerned the American and English literature from 1951 through 1953 and was published in the Annals of Internal Medicine, Volume 45, November and December, 1956. This Twelfth Review is concerned with the literature from 1954 and 1955. The editorial comments express the opinion of the authors of the Review, the Editorial Committee, and are not necessarily those of the Association.

Part II of this Review will be published in the March issue of this Journal.

Reprints can be obtained by sending $1.00 to Mr. G. W. Speyer, Executive Secretary, American Rheumatism Association, 10 Columbus Circle, New York 19, New York.

reactions of joints, muscles and related supporting tissue structures as listed in the foregoing table of contents.

General Incidence of Rheumatic Diseases

Social and Economic Importance

The need continues for well conducted, large scale epidemiologic studies on rheumatic disease incidence and the influence of various environmental, social and occupational and hereditary factors. Reported surveys have been either (a) large scale population studies which represent an adequate cross section of the public but lack a diagnostic accuracy, or (b) community, hospital or clinic surveys providing accurate diagnoses but inadequate population coverage.[526] Of the first type, the 1950–1951 Canadian Sickness Survey revealed that among the total national population of 15 million, there were 225,000 persons with arthritis or rheumatism; in 50,000 who were severely or totally incapacitated, rheumatic diseases were the sole or primary cause of disability. Of these, 68% were in the age group between 18 and 64. (Permanent Physical Disabilities, Pamphlet No. 6, Dominion Bureau of Statistics and Department of National Health and Welfare, Ottawa, 1955.) [1613] For this survey, trained lay enumerators personally visited 10,000 households distributed across Canada in metropolitan, small urban and rural areas; they obtained information from a household informant, usually the housewife. These statistics did not include a large number with mild or nondisabling rheumatic disorders, or those with rheumatic fever or its sequelae. Five U. S. Public Health Service surveys extending into 18 states, conducted over a 25-year period up to 1955, yielded the following data [412, 413] (table 1):

Of the 10,000,000 persons with some form of rheumatism in the United States, it was estimated that 4,500,000 actually had arthritis; [1044] at least 200,000 were totally and permanently disabled, and 800,000 were partially disabled. Medical expenditures, lost wages and direct subsidies approximated $700,000,000 annually.[216] Disability from rheumatoid arthritis was most severe in the juvenile form.[2155] In the Netherlands, with a population of 11,000,000, rheumatism affected 15% of men and 20% of women over 15 years of age. Of the more than 100,000 with rheumatoid arthritis or ankylosing spondylitis, at least 10,000 were "incurable invalids." Twenty per cent of all sick benefits were issued for rheumatic diseases, which resulted in the financial equivalent of 8,000,000 lost work days in 1953.[492] Rheumatic fever affected about 1,000,000 individuals in the United States, [686] though its mortality rate declined from six per 100,000 population in 1905 to 0.3 per 100,000 in 1953.[413]

Although industrial medical statistics were generally unsatisfactory, obviously rheumatic diseases pose a major industrial morbidity problem. Many of those affected continue to work, but the more disabled require some change of employment. The relationship between certain working conditions and incidence of certain rheumatic diseases did not necessarily prove causal.[1461] A thorough study in an English coal mining district indicated that miners suffered more frequent and more severe degenerative changes in the lower dorsal and lumbar intervertebral discs, knees and other joints than did control groups of other industrial workers. Trauma was a potent etiologic factor when present,

but these disorders also affected many miners with no history of injury. There was a close relationship between disc degeneration and duration of work involving heavy lifting and, to a lesser degree, prolonged stooping. Dampness and drafts did not apparently affect tissue degeneration but did influence the severity and incidence of pain and disability in those with disc degeneration; presumably drafts and dampness increased susceptibility to pain. For some unknown reason, osteoarthritis of the knees was more frequent in miners than in stevedores and light manual workers. The cause was apparently not related

TABLE 1

Incidence of Various Rheumatic Diseases: Effect on Disability and Hospitalization

		Arthritis and Chronic Rheumatism	Rheumatic Fever	Other Diseases of Bones, Joints and Locomotor Organs	Lumbago, Myalgia and Myositis	Backache
Annual Rates Per 1,000 Population	Total Case Rate	17.0	2.3	7.3	6.1	3.0
	Disabled Cases*	8.5	1.9	3.1	3.5	1.3
	Bed Cases†	5.3	1.5	1.7	2.2	0.78
Annual days of disability per 1,000 population		934	255.5	194.0	26.1	—
Mean days of disability per case		130.5	125.1	75.3	8.3	—
Annual hospital admissions per 1,000 population		0.59	0.17	0.72	—	—
Annual hospital days per 1,000 population		4.8	36.7	40.2	—	—
Mean days per hospital admission		12.1	168.7	61.3	—	—
Mean hospital days per case		—	54.3	46.7	—	—

* Unable to perform usual duties for one day or more.
† Confined to bed more than one day.
This information was collected by lay interviewers through repeated household visits, the diagnoses being checked when possible by correspondence with family physicians.

to distance walked at work, heavy lifting, dampness, drafts or kneeling at work. Overweight resulted in an increased incidence of degenerative changes in the knees as shown by radiographic examination. However, there was no correlation between obesity and the symptoms, signs or loss of time from work due to degenerative joint disease.[1222]

The medicolegal aspects of rheumatic diseases in industry were reviewed.[1836] Inconsistencies in interpretation of compensation legislation were discussed and proposals offered for revision of compensation regulations.[824] A complicated formula for measuring physical disability on the basis of a percentile depreciation from normal was advocated for assessment of industrial disability.[1886]

The socio-economic problems created by rheumatic diseases are of such magnitude that their solution requires mobilization of all available resources for research, prevention, case-finding, treatment, rehabilitation, home-care and fol-

low-up. This will necessitate coördinated planning and coöperation by the medical profession, hospital authorities, voluntary agencies, industrial and labor groups and all levels of government. The medical profession will need to re-evaluate the importance of intensive physical, psychologic, social and occupational rehabilitation. In many medical schools, undergraduate and postgraduate teaching in this field will have to be reorganized. Comprehensive rehabilitation services were recommended not only in hospitals but also in institutions for the chronically ill and disabled, in nursing homes, in rehabilitation centers and also in the homes of many patients whose rehabilitation could be accomplished more effectively in familiar surroundings than in an institution.[474, 526, 572, 686, 1172, 1432, 1461, 1743, 1765, 2155]

The development of facilities and services to combat complex social problems created by rheumatic diseases in the Netherlands was outlined by de Blecourt.[492] An account of the rehabilitation program of an English automotive firm illustrated the responsibility of industry and the practical contribution it can make to the successful reëstablishment of disabled workers.[2086] Reëvaluation of resort therapy was urged in a historical account of Pennsylvania's spas.[1160]

Special rheumatic disease units were advocated, and the organization of one such center in England was described.[75] [If "rheumatic disease centers" are established they should maintain, as far as possible, close contact with active treatment hospitals, with free access to consultation services of other specialties. In teaching centers, their staffs should participate actively in undergraduate and postgraduate training and research. Complete isolation of special patient groups carries an inherent danger of gradual withdrawal from the world of general medicine and its progress, with eventual deterioration in the quality of medical care.—Ed.]

Classification of Diseases of Joints and Related Structures

Inadequate knowledge of the cause and nature of many common rheumatic diseases creates imperfections and points of controversy in any classification devised to date.[526] Duthie[573] recommended that classification be confined to the simple groupings of entities which could be clearly defined. Even such apparently simple attempts at classification can present difficulties, as illustrated by a careful population survey conducted in Pittsburgh. Of 327 persons with "genuine rheumatic complaints," only one in eight fitted a classic description of any of the rheumatic diseases.[390] [This study emphasized the need for minimal diagnostic criteria and for limiting definitions which would draw sharp boundaries between the various rheumatic entities.—Ed.] An additional classification was proposed by a committee of the World Health Organization.[40]

Relative Frequency of the Rheumatic Diseases

Until clearcut diagnostic criteria are defined and generally accepted, statistical accuracy of the relative frequency of individual rheumatic diseases will be questionable, and surveys by different workers will have no uniform basis of comparison. In such surveys, even minor differences in definition may cause widely varying numbers of cases in any single diagnostic category.[390] Data from American industrial concerns indicate that the various forms of nonarticular rheumatism, degenerative joint disease, gout and rheumatoid and infectious arthritis were encountered in that order of frequency.[1461] In the future an even greater incidence of degenerative disorders may

be expected as the percentage of citizens in older age groups continues its rapid rise. In the United States between 1900 and 1950 the segment of the population over 65 years of age increased by 297%, while the general population increased only 98%.[1945] The decreased incidence of arthritis due to infection was attributed to the results of treatment with chemotherapeutic and antibiotic agents.[2135] [In the last few years there seems to have been an increase in infectious arthritis.—Ed.]

Diseases Primarily Related to Trauma

Acute Traumatic Lesions. Surgical treatment of contaminated wounds of the extremities was thoroughly reviewed. Adequate debridement of devitalized soft tissue with the conservation of viable skin, bone, tendon and nerve tissue was reconsidered. Delayed closure of contaminated wounds and secondary repair of nerves or tendons was advised. Even innocuous joint wounds demanded thorough exploration and excision of all detached bone, cartilage or foreign material, as well as the instillation of a suitable antibiotic and primary closure. Establishment of early joint mobility was essential as soon as infection was controlled, but weight bearing was to be avoided until motion and muscle strength had returned. The preservation of the ideal position for joint function prevented subsequent deformity or the need for corrective surgery.[257] Causalgia resulting from nerve injury required early recognition and treatment with sympathetic nerve blocks and, in some instances, ganglionectomy in addition to active physical therapy to avoid irreversible, disabling effects.[257, 1836] [One of us (D.C.G.) has been disappointed with the effects of sympathetic blocks in patients with causalgia.—Ed.]

In the experience of Hartung[926] direct trauma is a precipitating factor in tuberculous and gouty arthritis and in traumatic synovitis, including that superimposed on preëxisting osteoarthritis. The relationship of trauma to other forms of infectious arthritis, rheumatoid arthritis and rheumatic fever remains to be more clearly defined. [Trauma may be a localizing factor in infectious arthritis. A direct injury, such as a sprained ankle, may temporarily increase pain if that joint is already affected by rheumatoid arthritis. However, trauma never precipitates generalized rheumatoid arthritis.—Ed.]

Late Results of Trauma. The medicolegal aspects of trauma in producing or aggravating nonarticular rheumatism and osteoarthritis were reviewed. A conservative attitude, or "middle-of-the-road thinking," was advocated. It is justifiable to assume that various injuries, such as a lifting strain, may result in degenerative joint changes. Injuries such as intra-articular fractures or dislocations, penetrating wounds, and tears of cartilage or ligaments, which impaired joint structure or circulation, could be responsible for degenerative joint changes. In such instances, traumatic arthritis coming on after a period of weeks or months could not be distinguished from primary osteoarthritis which resulted after a period of months or years. A history of symptoms dating from the injury may be helpful in diagnosis.[568, 1836] Asymptomatic osteoarthritis was aggravated only temporarily by injury, but recuperation was slow because of the impaired healing processes in the older patients. The "all work or no work" policy of employers, insurance carriers and unions was considered to be unrealistic in the gradual rehabilitation of such patients.[1836] Repeated minor traumata were thought to be important in the production of nonarticular rheumatic lesions such as bursitis, capsulitis, tenosynovitis, and reflex sympathetic dystrophy. Minimal trauma was considered to be the responsible factor for

vertebral collapse in patients with an osteoporotic spine or with myeloma. Allergic arthritis as a complication of tetanus antitoxin or penicillin therapy of infected industrial wounds was also mentioned.[1836]

Two patients developed neuropathic joint disease after major trauma. One patient had syringomyelia and developed a Charcot's joint of the shoulder, while the other suffered a similar joint lesion following a cordotomy performed for the relief of pain due to tabes dorsalis.[184] [The latter may have been a tabetic neurotrophic joint. —Ed.]

The need for a more vivid appreciation of the risk of permanent and severe disability secondary to acute trauma was discussed.[171] Progressive fibrosis, and thickening of the joint capsules and ligaments with resulting contractures and deformities of joints produced by trauma, can be greatly minimized or wholly prevented by alert physicians and nurses, and by timely and intensive prophylactic physical therapy. The joints most susceptible to such secondary complications are the ankle, shoulder, elbow and metacarpophalangeal. [We agree that more emphasis on the prevention of superimposed joint disabilities following trauma is urgently needed.—Ed.]

Arthritis Due to Specific Infectious Agents

Since the introduction of effective antibiotics, the problem in infectious arthritis is becoming one of prompt recognition and adequate treatment. With the steady decline in infectious diseases and the equally steady improvement in therapeutic measures for controlling infections, arthritis as a complication of systemic infections is likely to become a clinical curiosity.[368] One notable area of failure has been the continuing incidence of pyogenic arthritis in premature infants and children.[510, 1783] [Rarely, staphylococcal infections follow intra-articular steroid injections.—Ed.]

Gonococcal Arthritis

The paucity of reports about gonorrheal arthritis indicates that penicillin is still effective therapy for gonorrheal infections. Arthritis, bursitis, and tenosynovitis occurred in 23 of 1,484 (1.5%) male patients who received chiefly local treatment for gonorrhea. Only five of 951 (0.5%) male patients treated with sulfonamides and none of 406 male patients treated with penicillin developed similar complications. Of 355 female patients, only nine (2.5%) developed arthritis or tenovaginitis following local treatment. None of 639 female patients developed such complications after sulfonamide or penicillin therapy. Ten of 25 male patients with gonococcal arthritis developed polyarthritis, while 15 had involvement of a single joint, i.e., knee, ankle, wrist, finger or shoulder.[1558]

The articular and nonarticular rheumatic complications of gonorrhea were reviewed.[49] Under the heading of "gonorrheal rheumatism" were included myositis, tenosynovitis, lumbar or plantar fasciitis, fibrositis of the neck and shoulders, perihepatitis producing costal or right shoulder pain, and periostitis with spurs of the os calcis. [An idea now discounted by most.—Ed.] When joint involvement occurred, it was polyarticular in 75% of the patients. Although no joint in the body was immune, the knee was most frequently affected; it was involved twice as often as the ankle, which was second in frequency.

"Vertebral arthritis" was also attributed to gonococcal toxins, and it was stated that "this is a very grave condition because of its liability to ankylosis and can be accompanied by a general fibrosis and ossification of the intervertebral ligaments."

[The occurrence of vertebral arthritis due to gonorrheal infection is not established. The changes described are more likely due to rheumatoid spondylitis or Reiter's syndrome. (J. J. B.)] In 85% of the patients the rheumatic complications were believed to result from the gonococcal toxins rather than from direct invasion by the gonococcus itself.[49] [We know of no evidence that "toxins" produce these lesions.—Ed.]

One patient who was treated with penicillin for an acute arthritis of the left knee (presumptively gonorrheal) proved through cultures and biopsy to have coccidioidomycosis.[1718] [Diligent search should be made for the gonococcus before starting penicillin therapy.—Ed.]

Instances of gonococcal arthritis developing 20 to 40 years after the primary infection continue to be reported.[49, 1758] One patient who had intermittent disabling attacks of joint pain for almost 30 years after an attack of gonorrhea was diagnosed as having chronic gonorrheal arthritis by radiographic findings of periostitis of the os calcis, spur formation, and dorsal tarsal arthritis.[1758] [The occurrence of chronic gonorrheal arthritis for years is doubtful. Reiter's syndrome, however, can be recurrent and is often associated with periosteal proliferation and spur formation.—Ed.]

Diagnosis. No new diagnostic procedures were suggested. The inconsistent behavior of the gonococcus in serologic testing was explained by the tendency of the organism to produce on culture various forms which were antigenically different by agglutination and agglutinin-absorption tests.[2235] [Reiter's syndrome closely resembles gonococcal arthritis. In patients in whom the bacteriologic findings, especially in the synovial fluid, are inconclusive, the diagnosis of Reiter's syndrome should be seriously considered. —Ed.]

Treatment. The use of penicillin has revolutionized the treatment of gonorrhea. Today uncomplicated gonorrhea is cured, with few exceptions, by one injection of penicillin (300,000 to 600,000 units).[1558] Nevertheless, arthritic complications still occur when the patient neglects to seek medical aid promptly or is unaware of the infection. Since complications do not develop when the original infection is eradicated, early treatment with an adequate dose of penicillin is indicated. If arthritis occurred, penicillin in a dose of 800,000 to 1,000,000 units daily for from seven to 10 days was usually adequate therapy. In a study of 57 patients with "chronic gonorrhea" and low back pain, a long-acting penicillin (N:N'-dibenzylethylenediamine dipenicillin G) was administered in doses of 600,000 units every four days for a total of 2,400,000 units, and the rate of cure as judged by a negative smear was 76%.[321]

Tuberculous Arthritis

Incidence. Although the incidence of tuberculosis is decreasing, 21 and 37 patients with tuberculous arthritis were discharged from a large New York City hospital in 1951 and 1952, respectively. These figures reflect an incidence of about 1.5% of the number of patients discharged with pulmonary tuberculosis, and about 0.06% of the total discharges in these two years.[926]

In Brazil, tuberculosis was still epidemic, and in Rio de Janeiro there were more than 100,000 patients with pulmonary tuberculosis. The relationship between the low standard of living and the incidence of tuberculosis (7.8% in the low income group compared to 3.4% in those of higher standards) was demonstrated, as was the frequency of bone and joint tuberculosis compared with that of pulmonary tuberculosis. The improvement in living conditions and hospital facilities and the introduction of the antituberculous drugs have reduced the mortality from 600 to 300 per 100,000 between 1920 and 1950.[328]

Clinical Data. In countries such as Brazil, where tuberculosis is epidemic, the primary complex is often followed by miliary tuberculosis, tuberculous meningitis, or by other disseminations without any intervening latent period.

Quite frequently this dissemination involves the skeleton.[328] While skeletal tuberculosis was considered to be metastatic from generalized disease[877, 1429] 286 of 500 patients (57.2%) with skeletal tuberculosis had no evidence of lung involvement.[328] Of 63 patients with normal lung findings, 36 developed pleural effusion after the onset of skeletal lesions in the spine.[2011] In another series, 80% of 34 patients had more than one type of tuberculosis in addition to skeletal lesions; the lungs or the genitourinary organs were most frequently involved. Fifteen per cent had polyarticular disease; the lower extremities (ankles and feet) were involved more frequently than was the spine. Trauma occurring four to eight weeks before the onset of skeletal disease appeared to be a significant precipitating factor.[926]

Campos[328] analyzed 1,000 cases of osteoarticular tuberculosis in Brazil. He places considerable emphasis on the ratio of lymphocytes to monocytes in the peripheral blood as an index of the patient's ability to withstand surgery. "A high lymphocyte/monocyte ratio is an indication of high resistance of the host and a favorable allergic condition; on the contrary, a low lymphocyte count and a high monocyte count is a sign of low resistance which places the patient in an unfavorable allergic condition." A lymphocyte/monocyte ratio greater than 5:1 was considered to be necessary to avoid the complications and hazards of surgical operations. This author accepts this ratio as having more prognostic value than does the sedimentation rate.[328] Tuberculous infection in joints was more frequently due to the human strain than to the bovine variety.[328, 1429]

The prognosis depended on tuberculous lesions elsewhere in the body[2222] and the variable state of tuberculous allergy as determined by the lymphocyte/monocyte ratio.[328]

Diagnosis. Early positive diagnosis was aided by synovial biopsy.[234, 926, 1326, 1649] Lymph node biopsy of the epitrochlear glands was of value in eight patients with synovial tuberculosis of the hand and the wrist,[1873] as was biopsy of the deep inguinal glands in tuberculosis of the hip.[1429] Soft tissue edema and joint effusion were the only early radiographic findings of tuberculosis.[926, 1636] [And were not diagnostic.—Ed.]

Special Locations. *Spine.* Spondylitis continued to be the most frequent and severe form of skeletal tuberculosis. Mortality was 30%, and before antibiotic therapy, unstable ankylosis in the thoracic region occurred in 58%.[2224] While streptomycin and isonicotinic acid hydrazide had a beneficial effect on the course of the disease and its local complications,[667, 871, 907] surgery was still the essential method of treatment. Spinal fusion before abscesses or paraplegias occurred,[328, 877] and costotransversectomy with evacuation of the abscess and curettage of the bony focus produced good results in 70 to 80% of patients.[328, 667, 871, 877, 2224]

Practically all patients with paraplegia were cured by constitutional treatment, immobilization and surgery,[328, 405, 667, 907, 1074, 2224] although occasional complications such as unstable ankylosis, paraplegia due to persistent abscesses, or spread of infection to adjacent vertebrae, required further surgical intervention.[907, 2046] Two patients developed tuberculous meningitis following a laminectomy for suspected protruded disc,[157] and one child had an unusual regeneration of a lumbar vertebra after treatment of a bony focus.[405]

Caution was advised when immobilized patients were treated with isonicotinic acid hydrazide because of further decalcification and possible vertebral collapse induced by the drug.[328] Of 100 patients with suspected tuberculous spondylitis treated

by surgical exploration, six were found to have chronic pyogenic spondylitis, and two others to have tumors.[667] Two patients with tuberculous granulomas of the thoracic spine were treated by drainage of the abscess, with recovery of neurologic function in one.[326]

Hips. In children an early and frequent sign of tuberculosis of the hip is early morning stiffness of the hip associated with a limp, which returns in the evening with fatigue. The hip is abducted, externally rotated, and apparently lengthened in the early stages, but later shortening occurs.[2234] Early diagnosis was established more frequently by biopsy of deep inguinal glands than by arthrotomy.[1429] Especially in children, antibiotics reduced the period of treatment and resulted in good function; in adults, the recovery of function was poor because destructive changes had usually occurred.[284, 871, 1074, 2010, 2222, 2223] In early involvement immobilization and antibiotic therapy resulted in recovery.[1074, 2010] Even in patients with more extensive involvement, immobilization and chemotherapy helped to preserve good function when combined with partial synovectomy and excision of diseased tissue.[284, 871, 1074, 2010, 2222, 2223]

Knees. Synovial tuberculosis of the knee joint was not infrequent. Partial synovectomy with removal of diseased tissue in addition to chemotherapy was considered by some to be the treatment of choice.[284, 809, 871, 1074, 2222] However, in synovial tuberculosis of the knee, especially in children and adults without an underlying bony focus, there was increasing evidence of successful treatment with bed-rest and systemic chemotherapy, supplemented in some instances with intra-articular streptomycin. The duration of conservative therapy was reduced by 50%, and the mobility of the joint retained was much greater than in the preantibiotic era in 11 patients,[2010] in 13 of 15 patients,[2222] and in 10 of 13 patients.[871] Arthrodesis was stated to be the treatment of choice in adults with bony involvement.[1074] One child with tuberculosis of the patella was treated with immobilization and patellectomy, but required an arthrodesis four years later.[1852]

Sacro-iliac Joint. Chemotherapy combined with arthrodesis was successful in eight patients; when it was combined with excision of sinuses and abscesses, five of six patients had satisfactory results.[871]

Trochanter and Bursae. Eleven patients, including five without a bony focus, were successfully treated by excision of the bursa; osteotomy in addition to excision was performed in five patients. However, six of these patients required subsequent surgery because of persistent disease.[871]

Other Lesions. Partial synovectomy with curettage of necrotic foci produced good functional results in lesions of the shoulder, elbow, wrist, and ankle joints.[2222] Three cases of multiple pseudocystic tuberculosis of bone were reported, one a rare occurrence in an adult. The etiology of this condition was not understood; however, it may have resulted from a bacillemia before tuberculin sensitivity had developed. It was characterized by very little constitutional reaction, the simultaneous onset of multiple lesions which were usually symmetric, and usually involvement of the long bones rather than of the short or flat bones. While cortical erosion with abscess and sinus formation was common, joint infection was uncommon, since the epiphyses acted as a barrier. The prognosis was favorable, and the response to chemotherapy was good.[385, 1505]

Treatment. Chemotherapy was highly effective in the treatment of joint and skeletal tuberculosis. While all agreed that it made possible early and safe surgical procedures, decreased the morbidity and mortality, shortened the need for hospital treatment, produced primary healing, and prevented local recurrences, there was still marked difference of opinion concerning the use of drug therapy alone, rather than combining it with surgery.

Animal studies proved that dihydrostreptomycin or isonicotinic acid hydrazide was very beneficial but did not produce a histologic cure.[1475] After 90 days of streptomycin therapy there was still evidence of infection in 14 of 22 patients with synovial tuberculosis, and in 13 of 15 patients with bony involvement.[2222] [A longer period of treatment, ranging from at least six months to one year, with combined drug therapy, is generally indicated.—Ed.]

There were frequent reports that synovial tuberculosis (especially in children) and soft tissue infection responded in a remarkably satisfactory manner to bed-rest added to chemotherapy. These reports also emphasized that recovery of joint function was better than in the prechemotherapeutic era.[234, 235, 309, 549, 871, 1588, 1932, 2010, 2222, 2223]

Treatment with more than one drug (streptomycin, isonicotinic acid hydrazide, or para-aminosalicylic acid) was advised.[284, 328, 1429, 2010, 2222, 2223] Isonicotinic acid hydrazide was believed to be more effective than streptomycin in the therapy of skeletal lesions;[328, 1429] iproniazid produced much greater systemic improvement and skeletal recovery than did isoniazid.[235] [But this drug may have more toxicity.—Ed.]

Surgery, in combination with the above drugs, was still an essential part of treatment of joint and skeletal tuberculosis. Fusion of the spine, drainage of abscesses, excision of necrotic tissue, and synovectomy or arthrodesis of joints were necessary to produce functional recovery.[284, 309, 328, 549, 667, 871, 877, 907, 926, 962, 1074, 1326, 1429, 1588, 1932, 2010, 2222]

Tuberculous Rheumatism (Poncet's Disease)

The concept of tuberculous rheumatism as distinct from tuberculous arthritis was originally presented by Poncet. This designation is rarely used, and no articles on this subject appeared in the literature covered in this Review. One patient was reported to have joint exacerbation after the hypodermic injection of 1:100,000 solution of tuberculin.[1753] One observer stated: "The condition must be rare if it exists at all. I have never seen a case that I could call tuberculous rheumatism." [We agree.—Ed.]

Typhoid Arthritis

One patient with probable "typhoid spine" was reported. Diagnosis was based on a positive stool culture and radiographic evidence of a destructive lesion of L2 and L3. Spinal fusion of L1 through L3 apparently arrested the disease. Chloromycetin was not utilized in this case, but the authors believe that it would have hastened the resolution of the disease.[1140] [Today, typhoid fever is a rarity, and joint involvement is apt to be regarded as a relic of the past. The fact that case reports continue to appear should serve as a reminder that this disease must still enter into the differential diagnosis of unusual lesions of the spine.—Ed.]

Brucellosis

Since World War II the number of cases of human brucellosis in the United States has progressively declined, largely because of an intensive educational program to eliminate the disease in cattle. The exact number of active cases was impossible to determine, but 40,000 appeared to be a reasonable figure.[1978]

Etiology and Epidemiology. Brucellosis is basically a disease of animals, and is very rarely transmitted from human to human. Among the three species

of the genus *Brucella* there exist fundamental differences that have major clinical significance. *B. melitensis* is the most invasive and produces a severe illness in man. Of the human cases of brucellosis in the United States, less than 10% are due to *B. melitensis,* but in the world at large this species is the most common cause of brucellosis. Another 10 to 20% of the cases of human brucellosis in the United States are due to *B. suis,* for which the natural reservoir is the hog. The most frequent source of human brucellosis in the United States is *B. abortus,* which causes about 75% to 80% of all cases. Approximately 25% of the latter cases may be related to the drinking of raw milk, and the remainder to direct contact with cattle or swine, or their tissues or body fluids. The organism readily gains entrance through minute abrasions of the skin, through mucous membranes of the eye, and probably through the nasopharynx. Young animals and children, although frequently exposed to Brucella, have a low incidence of infection.[254, 1243, 1978]

The Brucella organism localizes in those tissues having an abundance of reticuloendothelial cells, especially the bone marrow, lymph nodes, liver and spleen. The bacteria invade the cells and possibly proliferate within the macrophages. The incubation period in the average case varies from a few to 21 days, but in an occasional case several months may elapse between the time of exposure and the first appearance of symptoms.

Symptoms Referable to Joints and Muscles. Generalized aches, backache and joint pains are outstanding clinical manifestations, along with weakness, sweats, chills, headaches and anorexia. Bone and muscle pains were present in 65 of 94 (69%) culturally proved cases of brucellosis due to *B. abortus.* It was noted that definite pain and tenderness over bone and joints usually indicated the presence of localized involvement.

Localized Bone and Joint Lesions. Spondylitis and arthritis were the most frequent complications of brucella infection.[254, 1348, 1978] Back symptoms due to this disease mimic the manifestations of ruptured intervertebral disc.[1978] Signs of musculoskeletal involvement were analyzed in 94 cases of *B. abortus:* tenderness over the spine was present in six patients (6.4%); pain over the hip joints was observed in two (2.1%); and pain over the sacro-iliac joint in one (1.0%). Prepatellar bursitis was due to *B. abortus* in four patients, one of whom had a 14-year history of involvement.[1050] Chronic brucellosis has not been found to be the cause of rheumatoid polyarthritis.[1978]

Typical involvement was an osteomyelitis of the spine, long bones or pelvis. This lesion developed in the bone marrow from a localized Brucella granuloma, then infiltrated the bone and surrounding soft tissue such as the intervertebral disc. Both bone and disc were destroyed by the granulation tissue, with formation of pus in some cases.[254]

Diagnosis. The recognition of brucellosis is often first suggested by joint and muscle aches and pains, occurring with fever, in farmers, livestock producers, veterinarians, or employees in meat-packing plants. The precise diagnosis is absolutely dependent upon serologic and cultural evidence. [Especially the latter.—Ed.] With the widespread use of antibacterial therapeutic agents for even the mildest febrile disease, experienced investigators find it increasingly necessary to depend more and more upon serologic procedures, and less upon bacteriologic results. Nevertheless, an attempt should still be made to clinch the diagnosis by isolating the organism from blood, excised tissue, bone marrow

or body fluids. Special culture media are necessary. In some instances, cultures of aspirated sternal marrow will yield Brucella when simultaneous specimens of venous blood remain sterile.

The serum agglutination test was agreed to be of considerable diagnostic significance; in both acute and chronic brucellosis the titer of agglutinins in the vast majority of cases is 1:100 or more.[254, 1050, 1978] The urgent need for a standardized antigen and a technic for general use was discussed.[1978] Little or no additional diagnostic aid was thought to result from the complement fixation test, which is tedious and more exacting than the agglutination test. The opsonocytophagic test was not recommended for the routine diagnostic laboratory. Intradermal skin tests using various preparations of Brucella antigens are of dubious value in the diagnosis of the suspected sporadic case of brucellosis.

Treatment. The most successful treatment consisted of a daily dose of 2 gm. of chlortetracycline or oxytetracycline in combination with 1 to 2 gm. of dihydrostreptomycin (or streptomycin) for 21 days.[254, 1978] The above schedule was repeated when relapses (20%) occurred. Corticotropin or cortisone given for short periods was of dramatic benefit to the seriously ill patient.[1978] Erythromycin was reported to be effective in 14 patients, including acute and chronic cases. Twelve of these 14 patients were observed, to determine the percentage of relapses following treatment with 20 to 30 gm. of erythromycin given in a nine- to 16-day interval. Five patients again became febrile, and developed positive blood cultures and high agglutination titers. However, during relapses these patients responded as well to erythromycin as they had in the initial febrile period.[2122] Excision of the infected tissue cured four patients with patellar bursitis.[1050] Bed-rest, orthopedic aids such as casts and braces, and, rarely, surgical procedures were required in some patients with spine or joint involvement.[254, 1348, 1978]

[Tetracycline has not had an adequate trial but may prove more effective than its derivatives.—Ed.]

Suppurative Arthritis

In Infants. The occurrence of acute suppurative arthritis in premature infants and in children under one year of age presented a very serious and urgent problem.[510, 1783] The systemic reactions are so deceptively mild that early diagnosis is too often not made and irreparable damage to the joints occurs. In five premature infants the diagnosis of pyogenic arthritis of the hip was delayed from six days to 16 months; the delay resulted in complete destruction of the head and the neck of the femur in four patients.[1783] The average age at the onset of symptoms in this group was 12 days. The following suggestions for an early diagnosis were made: aspiration of the hip joint should be considered when an infant presents with swelling of the leg, thigh, buttock or groin, and any infant with a severe infection should be tested daily for the possibility of septic hip arthritis. Acute suppurative arthritis in these newborn infants and young children is usually confined to a single joint, most often the hip joint (65%), sometimes the shoulder, and other joints rarely.[510] The shoulder joint was involved in three infants[510] and the knee joint in one child.[876] Systemic reaction was described as mild, and early roentgenograms may not reveal widening of the joint space or dislocation, but may show within a few days a soft-tissue shadow in the region of the joint.[510, 1783]

Bacteriology. The causative organisms may be any pyogenic bacteria, but in the great majority of cases streptococci or staphylococci.[510] In cultures taken from three of five premature infants with acute suppurative disease of the hip, the organism identified was *Micrococcus pyogenes* var. *aureus*.[1783] Primary pneumococcal arthritis of the hip caused by a type XII pneumococcus was the basis of one report.[1244] Inflammation of the synovial membrane from hematogenous spread with purulent effusion due to meningococci, and very rarely to *Salmonella typhi*, and by extension from adjacent foci of osteomyelitis, was again listed among the causes for suppurative arthritis.[365]

Treatment. The prompt aspiration of the purulent exudate and the instillation into the joint of an antibiotic chosen on the basis of sensitivity studies, plus systemic antibiotic therapy, were emphasized as the only effective method for preventing extensive crippling sequelae.[285, 286, 510, 1205, 1783] [Aspiration is essential, but systemic antibiotics without intra-articular injections are usually adequate. —Ed.] When treatment is delayed until changes are visible in the roentgenogram, some degree of permanent joint damage has usually occurred.[1783] The following program of treatment was recommended:[510] immediate intra-articular injection of 100,000 units of penicillin as soon as a provisional diagnosis is made, repeated daily until the sensitivity of the organisms to the various antibiotics is established. If pus is already present, the joint is irrigated with a solution of 1,000,000 units of penicillin in 1,000 c.c. of normal saline for from eight to 10 days. The limb is immobilized and traction applied if the hip is the site of involvement. Systemic antibiotic therapy, continued for an average of 21 days or a minimum of five days after all evidence of activity has subsided, was recommended. Surgical intervention was necessary when sequestration of adjacent bone occurred. The value of repeated aspiration of the joint to prevent cartilage destruction from the proteolytic enzymes in the pus was reported.[1244] One adult with pneumococcal arthritis of the hip and a positive blood culture made a recovery following the use of 600,000 units of crystalline penicillin given parenterally every six hours for a period of four weeks.[1244]

An investigation of poor end-results was found to be due to improper selection of the antibiotics used early, and inadequate surgical drainage in the fully developed acute and walled-off chronic pyogenic lesions.[285] [This author restricted himself to the oral use of the broad spectrum antibiotics.—Ed.]

Oxytetracycline has been successfully used in both acute and chronic cases of pyogenic arthritis and osteomyelitis, as well as prophylactically in the treatment of traumatic lesions of the bones and joints.[286] Chlortetracycline, carbomycin and tetramycin have also been used with equal effectiveness, depending upon the sensitivities of the organisms encountered.

Six of 55 patients who had replacement prosthesis operations on the hip developed staphylococcus infections subsequent to the operation, and, of these, four were patients who had had sepsis before the operation. From this experience it was concluded that patients with prior sepsis should not be considered for this procedure. Prompt removal of the prothesis, in addition to use of suitable antibiotics, was necessary to salvage the hip joint; the resultant pseudarthrosis restored four of the six patients to useful life.[1637]

Neurosurgical intervention proved to be effective in the management of 10 patients with epidural granulomas of the mid-dorsal spine.[326] The causative

infectious agent was staphylococcus in six patients, tuberculosis in two, torulosis in one and syphilis in one. These lesions produced a definite clinical syndrome of boring back pain, radiculitis and spinal cord damage as a result of vertebral osteomyelitis or direct extension of the infection from adjacent structures. Roentgen manifestations, including myelographic findings, correlated with the clinical aspects and permitted a more precise diagnosis. [Information on the antibiotics used was not reported.—Ed.]

Syphilitic Arthritis

Primary or secondary syphilis was capable of mimicking any type of acute or chronic arthritis. Among the common manifestations of the various stages of syphilis were myalgias, myositis, osteitis, periostitis, bursitis, gummatous lesions of muscles and periarticular tissues, and osteomyelitis, as well as the neuropathic joints (Charcot's joints) which are secondary to syphilitic lesions of the central nervous system.[49] ["Charcot's joints" are not actually a form of syphilitic arthritis, and will be discussed in the section dealing with neurotrophic arthropathies.—Ed.]

An epidural granuloma due to tertiary syphilis produced a cord compression syndrome which was relieved by excision of granulation tissue from D1 to D4.[326] In this report the clinical and roentgen aspects of nine additional cases of epidural granulomas were presented.

Mycotic Diseases of the Joints

Coccidioidomycosis. For several decades coccidioidomycosis has been recognized as endemic in the southwestern United States, Mexico and South America, but as a result of rapid modern transportation this disease is being diagnosed with increasing frequency in many parts of this country.[1718, 1966] In the second, or disseminated, stage of the illness, bone and joint involvement is common and may be readily confused with the musculoskeletal manifestations of tuberculosis.[1966]

The primary phase of the disease is usually a self-limited pulmonary infection due to the inhalation of the fungus *Coccidioides immitis,* and is characterized by malaise, anorexia, chills, fever, headache, night sweats and pleurisy. Joint symptoms, including pain, tenderness, and slight swelling without effusion, occur in one third of all pulmonary cases. This is the so-called "desert rheumatism."[1966]

It was estimated that dissemination occurred in less than 0.2% of patients with the benign pulmonary infection.[832, 1385] This complication usually takes place within the first few weeks or months, and often leads to death. In one series of 22 cases,[1385] the mortality was 12.5% in those of the Caucasian race, while among the Negroes the mortality was 77%. Practically every organ and all bones and joints of the body were involved by the granulomatous lesions of this phase.[407, 1385]

Osseous and Joint Lesions. The osseous lesions have a predilection for bony prominences, and also for the short bones of the hands and feet, spine, ribs, scapulae and clavicles. The initial involvement usually occurs near the ends of the long bones. The lesions were again described as primarily destructive, with frequent

periosteal proliferation, cortical expansion, soft tissue abscesses, and extension into adjacent joints.[1385, 1966] The roentgenographic findings due to such bone changes were helpful in the differential diagnosis between this disease and tuberculosis, which frequently involves only the joints.

Eleven of 22 patients with coccidioidomycosis of the skeletal system died after an average of only 8.3 months of hospitalization. Among these were 10 of 13 Negro patients, but only one of the nine white patients.[1385]

Invasion of a single bone or joint was considered to be unusual;[1385, 1718] however, synovitis of the knee was reported in three patients.[1966, 2080] Tenosynovitis of the right wrist and hand and trochanteric bursitis occurred in one patient.[2159] No adjacent bone lesion was found in this group of four patients. One patient with a monostotic lesion of the calcaneus[832] and four unusually severe, disseminated cases in children[407] were described.

Diagnosis. There was agreement that there is no pathognomonic clinical or roentgen finding, and that positive diagnosis can be made only by identification of the organism. A positive skin test was thought to be fairly reliable,[1385] but only six weeks or more after the primary infection. It is often negative with disseminated disease. A negative skin test early, followed by a positive skin test later, is conclusive. The complement fixation test (1:32 or greater) indicated dissemination of the disease. Positive diagnosis was established by the demonstration of the spherules in gastric washings, sputum, pleural or spinal fluid pus and synovia. The following criteria were listed as helpful in differentiating between the bone lesions of coccidioidal and tuberculous infections:

1. Tuberculosis does not have a predilection for bony prominences.
2. Tuberculosis does not often have skin manifestations.
3. Tuberculosis is frequently found in joints alone, coccidioidomycosis infrequently.
4. Tuberculosis generally causes less destruction of juxta-articular bone.
5. Tuberculosis is likely to show destruction of nonopposing cartilaginous surfaces, coccidioidomycosis, of opposing cartilaginous surfaces.
6. Tuberculosis of joints usually takes many months to develop, while coccidioidal infections may progress much more rapidly.

Treatment. No specific therapy is known, but many drugs were used; prodigiosin and fungicidin (Mystatin);[1385] 2-hydroxy-stilbamidine;[832] ethyl vanillate;[407, 1966] cinnamic acid, Actidione, and sassafras tea.[407] Ethyl vanillate (ethyl 4-hydroxy-3-methoxybenzoate) therapy usually requires several months, but its results appeared to be encouraging. Synovectomy and excision of the diseased soft tissue where there was no underlying bone infection apparently arrested the disease in four patients.[1966, 2080, 2159] Amputation of a severe focus in an extremity was believed to have been a life-saving procedure in two patients.[1385] [Amphotericin B given intravenously and intra-articularly may be of value in patients with joint involvement.—Ed.]

Histoplasmosis. Bone and joint involvement with *Histoplasma capsulatum* is rare. The clinical and pathologic findings in 20 cases were reviewed.[2145] Muscle and joint pains occurred in seven patients, but no lesions in bones or joints were demonstrated. Most frequently involved were the lungs, then the oropharynx, liver, spleen, lymph nodes and adrenal glands. The incidence of disseminated disease and mortality in this study was unusually high: 11 of the 20 patients died. The appearance of the organism on direct smear and in

histologic sections is quite characteristic, but confirmation by bacteriologic methods should be used for definite diagnosis.

Blastomycosis. One Negro patient who had moved from North Carolina to Philadelphia died of acute fulminating systemic blastomycosis of only three months' duration. While the initial symptoms were pneumonic, diagnosis was made by a smear of purulent joint fluid. The organism was demonstrated in the myocardium, lungs and spleen; the only osseous or joint involvement was in the left knee joint. Treatment in this patient consisted of bed-rest, oxytetracycline, cortisone and stilbamidine.[1364] [Recently a less toxic analogue, 2-hydroxystilbamidine, has been used successfully in the treatment of systemic blastomycosis. —Ed.]

Actinomycosis. With the advent of the sulfonamides and antibiotics, the treatment of actinomycosis has improved considerably. One patient with actinomycosis of the temporomandibular joint was cured by a combination of surgical drainage, oral tetracycline therapy and neomycin irrigations.[967] Full use should be made of the bacteriologic and sensitivity tests now available to confirm early diagnosis and aid in effecting an early cure.

Cryptococcosis (Torulosis, European Blastomycosis). Bone lesions in cryptococcosis are rarer than in the other systemic fungus diseases. They were observed in 17 of 200 patients.[414] One patient with initial symptoms of pain and localized swelling of the lumbar spine had an osteolytic lesion of the spinous process of the third lumbar vertebra and an extensive but asymptomatic infiltration of both lungs on a routine roentgenogram of the chest. The organism *Cryptococcus neoformans* was cultured from pus obtained by aspiration of a mass overlying the third lumbar vertebra. The patient is believed to be the first to be reported from Canada, and was apparently cured by aspiration of the soft tissue abscess, followed by sulfadiazine therapy and eventual excision of the infected spinous process.[613] Another patient, after eight months of back pain, developed weakness and neurologic findings in both lower extremities. Roentgenograms showed osteolytic destruction of the bodies and neural arches of D4 to 6, extension into the vertebral end of the fifth rib, and an osteolytic lesion of the left frontal bone. After laminectomy and biopsy of the epidural abscess, which revealed *C. neoformans*, the neurologic symptoms were improved.[326]

The usual portal of entry is the respiratory tract, but the gastrointestinal tract and skin have also been suggested as possible sites of entry. While it is possible that pulmonary cryptococcosis may occur in a mild, spontaneously healing form, it is usually a progressive disease with a marked predilection for central nervous system involvement, lasting several years and eventually proving fatal. [Cryptococcosis has not been reviewed previously. It is believed to be worldwide in distribution, and has been reported throughout the southern United States from Florida to California. While there has been no specific therapy in the past for five of the major mycotic diseases (coccidioidomycosis, histoplasmosis, blastomycosis, cryptococcosis and moniliasis), successful treatment of this group of infections has been reported recently with a new antibiotic, amphotericin.—Ed.]

Rarer Forms of Specific Infectious Arthritis

Leprosy. An excellent review described the various types of bone lesions, the radiographic appearance, and the necessary treatment in 108 of 116 patients with leprosy. Lesions of destructive type (41% of the patients) were believed due to

the action of *Mucobacterium leprae* in the reticuloendothelial system. The absorptive bony lesions which occurred in 90% of the patients were related to the soft tissue infections associated with neurotropic lesions. Trauma and defects in the peripheral vascular circulation, as demonstrated by serial angiograms, were also related to the bony lesions.[1589]

Miscellaneous Others. Nine patients were reported with osteitis pubis following bladder or prostate surgery. One patient developed a "destructive" arthritis of the hip joint despite prompt response of the initial pubic and ischiatic lesions to roentgen therapy.[1205] One patient with osteomyelitis of the lumbar spine due to *Salmonella choleraesuis* septicemia was probably improved by chloramphenicol therapy and a plaster jacket.[1033]

Polyarthritis occurring as a complication in five of 37 patients with rubella (German measles) was described, and the literature on this subject was reviewed.[1255] [This relationship has seldom been reported in the American literature to the date of this review. The occurrence of 10 cases of rubella arthritis in Massachusetts in 1957 with negative latex fixation tests for the "rheumatoid factor" is worthy of note.] [1056]

Rheumatic Fever

Occurrence. Authors from Mexico,[1807] Sweden,[174] the Netherlands [493] and the United States [2161] reëmphasized that rheumatic fever is a worldwide problem, though its greatest reported incidence is still in the United Kingdom and the United States.[2183] With data from excellent sources, there was reconfirmation of the impression that a significant reduction in childhood mortality from rheumatic fever and rheumatic heart disease occurred from 1940 to 1950.[2161] In that interval in New York City there was a 74% decrease in mortality due to rheumatic fever in the white population; among the nonwhites the few available figures suggested a downward trend.

In the same 11-year period there was an 82% decrease in mortality due to rheumatic heart disease of *all* children under 20 years, but in 1950 the mortality rates of the nonwhite groups were still three to four times those of the white groups involved.

Predisposing Factors Governing Incidence. No new predisposing factors have been discovered. In a Dutch survey,[493] dampness in the dwelling, the most ancient of supposed causes, was thought to contribute to the increased occurrence of rheumatic diseases. [Rheumatic fever not specified exactly.—Ed.]

Season. Although, in general, chronic diseases show few seasonal variations, a specific chronic disease such as rheumatic fever has a distinct seasonal variation. In the United States, a survey [412, 413] reëmphasized that the climb in the incidence of rheumatic fever was slow during the fall months, but rapid from January to April, reaching a peak in the latter month and then falling rapidly.

In Mexico, on the other hand,[1807] the lowest incidence of rheumatic fever occurs during the winter months. The major portion of attacks takes place during the middle and end of summer, the peak month being August. [It is established that the monthly incidence of β-hemolytic streptococci in throat cultures parallels the clinical incidence of rheumatic fever.—Ed.

Social and Hygienic Factors. A Mexican study [1807] concluded that rheumatic fever and rheumatic heart disease were considerably more prevalent in the lower socio-economic classes than in the upper classes. [This observation is in accord with previous studies showing that the social distribution of the disease can be correlated with the incidence of streptococcal infections in any socio-economic group.—Ed.]

Family, Heredity, Constitution. A genetic analysis corroborates the suggestion

that rheumatic fever susceptibility is inherited as a simple recessive trait.[1991] The evidence for the recessive inheritance was reinforced somewhat by a report of the insignificant number of cases of rheumatic fever (three in 239 families) when *one* parent was nonrheumatic and was known not to have close kin who were rheumatic. (Groups studied were from a clinic population in New York City.) This means that *children* of *two affected parents* would *all* be susceptible to the disease; of *one affected parent* and *one carrier*, one-half would be susceptible; of one affected parent and a noncarrier, none would be susceptible; of two carriers, but not affected parents, fewer than one fourth would be susceptible.[2237] However, one study [2008] demonstrated that the attack rate of rheumatic fever in young adults with streptococcal infection was approximately the same among those who did and those who did not have a family history of rheumatic fever. [It appears as though a susceptibility may be behaving as a simple mendelian recessive, but the exact mode of inheritance remains totally obscure—Ed.]

Sex. In Sweden, in the city of Malmo, it was found that a preponderance of patients with rheumatic fever and rheumatic heart disease was female.[174] [The study was highly selective.—Ed.] In Mexico, the female sex was also more frequently affected, in an almost 2:1 ratio.[1807]

Age. In one Swedish study [174] it was noted that a higher incidence of first attacks of rheumatic fever occurred in adult groups, but, as indicated above, this study was a highly selective one. Another observer from the same country [607] stated that the age frequency curve for rheumatic fever showed a marked peak at 20 years, approximately one-half of the cases having their initial attack before this age. Cases above age 40 were less common, but nevertheless did occur. [Several of us are impressed with the frequency of acute rheumatic fever in the middle and older age groups. This is not the exceeding rarity which we were previously given to believe.—Ed.]

Race. Rheumatic fever and rheumatic heart disease are widespread in Mexico, notwithstanding a mixed population of whites and Indians.[1807] Reports concerning rheumatic fever from many countries indicate that it occurs in all races.

General Clinical Data and Relative Incidence of Clinical Manifestations. The absence of a diagnostic test for rheumatic fever makes for uncertainty in analyzing clinical data [530] and, in the absence of the classic major and minor features of rheumatic fever at any one point in time, the basis for a diagnosis is often hopelessly lacking.

The rash of rheumatic fever, erythema marginatum (or annulare), is said to be specifically diagnostic of rheumatic fever,[346, 1463, 1909] but a disciplined study [298] stressed simply that rheumatic fever and erythema marginatum continue to be related in some way. Since erythema marginatum is also described as occurring in patients with bronchiectasis and acute nephritis, unassociated with rheumatic fever, it is therefore a nonspeeific phenomenon.

It was pointed out in several reviews [346, 1463, 1909] that rheumatic nodules are subcutaneous and usually occur only during florid rheumatic fever; rarely are they the only manifestation of rheumatic activity.

An excellent article [795] concerned with a variety of ocular signs and symptoms in the "collagen diseases" stressed that in rheumatic fever 5 to 7% of the cases studied had uniocular or binocular phlyctenular conjunctivitis, episcleritis, scleritis, tenonitis or iritis. [This incidence is higher than most of us have witnessed.—Ed.] The first three are morphologically analogous expressions of the same pathologic process, differing only topographically. The microscopic structure of the phlyctenule is identical with that of Aschoff's nodule on the heart.

Some elaborate, negative studies were done on the relationship of nutrition to rheumatic fever.[2216, 2217, 2218, 2219] [The authors seemed to lack an appropriate frame of reference in tackling the problem of rheumatic fever.—Ed.]

Assuming that the physiologic effect or additional strain of chronic anxiety may be especially significant when the heart is already crippled by disease, one group[1073] tried to deal definitively with the anxiety discovered in children convalescing from rheumatic fever. [The paper itself does no more than describe some anxious children who have rheumatic heart disease.—Ed.]

Pathology

If fusion of aortic valve commissures and thickening of chordae tendineae were taken as criteria, 61% of an unselected group of 500 autopsies revealed evidence of rheumatic endocarditis.[656] However, only 363 (3.7%) in another series of nearly 9,900 autopsies performed during a 17-year period showed macroscopic rheumatic cardiac lesions; 163 of these cases had no history of acute rheumatic fever.[606] Of particular interest in this study was the occurrence of two cases with amyloid nephrosis.

The significance of the Aschoff's body in rheumatic heart disease was the subject of several studies. The morphologic features of the Aschoff's giant cell were reviewed;[2152] pathologic studies led to the conclusion that this cell was derived from connective tissue elements and not from myocardial fibers.[1791, 2152] Nonrheumatic giant cells developing from damaged myofibers were described as a nonspecific attempt at regeneration.[2152]

Aschoff's bodies in the left atrial appendage biopsied at the time of mitral valve commissurotomy were reported in 18.8 to 50% of patients with apparently inactive rheumatic heart disease.[375, 628, 636, 1319, 1342, 2070, 2107] [This difference of incidence may be due to variation in criteria for diagnosis of the Aschoff's body and/or the composition of the group studied.—Ed.] In spite of the statement that patients had clinically *inactive* rheumatic heart disease, erythrocyte sedimentation rates (ESR) were said to be elevated in some patients of each of two study groups.[2070, 2107] The frequency of appearance of Aschoff's bodies was felt to have positive correlation with ESR in one group,[2070] and a negative correlation in the other.[2107] There was agreement that Aschoff's bodies appeared more frequently in younger patients.[375, 1319, 2070] These lesions were detected with equal frequency in patients with and without evidence of recent streptococcal infection.[636, 2107] Postoperative mobility, mortality, clinical improvement, and probable reactivation of rheumatic fever bore no relationship to the finding of Aschoff's bodies in the biopsy.[375, 1342, 2070, 2107] Such changes were not seen in control groups of patients.[375, 1342] There was suggestive evidence that the atrial appendage biopsy taken at the time of operation may not yield a sample representative of Aschoff's bodies in the entire heart.[1319]

The lack of correlation between clinical evaluation of rheumatic activity and the presence of Aschoff's bodies in the left atrial appendage has led some to question the old precept that the Aschoff's body per se is a sign of rheumatic activity. They suggest that it merely represents a phase of a specific tissue response of cardiac connective tissue in rheumatic fever.[2070] [This seems an unlikely explanation.—Ed.]

Laboratory Data

Electrocardiographic Studies. The electrocardiograms of 62 patients with acute rheumatic fever were analyzed with respect to (1) abnormal P waves, (2) PR interval, (3) ST segment and T wave changes, and (4) QT interval.[675] Changes in the ST segment and T wave, present in 41.8% of cases, were stressed as most helpful in the diagnosis of rheumatic carditis. The importance of serial records was reëmphasized. Abnormalities in the QT interval were noted in 75% of rheumatic fever patients in one series,[851] and in 26.3% in another series.[338]

In a group of 110 patients with scarlet fever treated with penicillin, 10 showed prolongation of conduction by electrocardiographic studies.[2190] When the cardiac status of these subjects was evaluated seven years later, none of those without electrocardiographic changes at the time of the scarlet fever infection had any evidence of cardiac disease; however, of those 10 patients who seven years earlier had prolonged PR and QT intervals, eight (80%) had definite or "probable" rheumatic heart disease. The data tend to validate the abnormal electrocardiogram as an important criterion for the diagnosis of rheumatic fever in a patient with proved streptococcal pharyngitis.

Controversy concerning the significance of the QTc determination has centered about the failure to agree on a technic of measurement. A chart relating the QT interval to the cardiac rate was presented[2063] to simplify the determination of the QTc, which these authors regard as a sensitive diagnostic measurement of active carditis.

Sedimentation Rate and Alterations in Serum Proteins. It is worthy of reëmphasis that there is no specific diagnostic test for acute rheumatic fever.[772, 1403, 1792, 1875, 2249] C-reactive protein (CRP) has been studied extensively and its importance as a reflection of rheumatic activity confirmed. It is considered by some workers to be superior to other indices of inflammation because of fewer "false-positive reactions"[1740] and more rapid response to the appearance or disappearance of rheumatic activity.[1875] [These are not unanimous views.—Ed.] No correlation could be made between CRP and the presence or absence of Aschoff's nodules in amputated auricular appendages of rheumatic patients undergoing mitral commissurotomy.[624] The effect of anti-inflammatory agents (cortisone, ACTH and salicylates) on the disappearance of CRP is most probably brought about indirectly by the subsidence of inflammation, rather than by a direct effect on the abnormal protein.[2021] Further characterization of CRP by starch electrophoresis revealed it to be a gamma globulin,[2250] and gel diffusion studies indicated the presence of at least three antigenic components in crystalline CRP.[624, 1263]

Serum electrophoresis in patients with acute rheumatic fever confirmed the nonspecific abnormalities of the alpha, beta and gamma globulins.[779, 1167] It was stressed that increased beta globulin was more frequently a feature of rheumatic inflammation than of nonrheumatic inflammation. But this increase is not sufficiently specific to justify its use as a diagnostic test. Increased gamma globulin in the serum of rheumatic fever patients was shown to be reduced by administration of aspirin, cortisone and ACTH.[2029]

Serum mucoprotein was abnormally increased in 15 of 17 patients with rheumatic fever.[837] The presence of elevated mucoprotein levels correlates well with other

evidence of rheumatic activity, but is no more specific: "There is little reason to prefer mucoprotein determinations to such an easily performed procedure as the sedimentation rate." [836]

Fibrinogen levels as determined by the clot density technic paralleled the changes in the CRP and the clinical course of acute rheumatic fever, and were often the first abnormal phenomena to normalize with subsidence of rheumatic activity.[1298] A test demonstrating "accelerated fibrinogen polymerization" in patients with rheumatic fever was discussed.[1299]

The subject of antibodies to extracellular products of group A streptococci was reviewed.[2249] In 92 to 95% of patients the antistreptolysin O (ASO) titer rose to diagnostic levels at some time during the course of acute rheumatic fever.[1403, 2249] [Elevated titers indicate recent streptococcal infection, not the presence of acute rheumatic fever.—Ed.] If more than one antibody is measured (i.e., antistreptokinase and antihyaluronidase in addition to the ASO), an unequivocal response can be shown in almost all cases. Rheumatic fever patients treated with aspirin, cortisone or ACTH showed a more rapid decrease in ASO titer than did a control group.[2029] Modifications of the standard ASO test were described.[451, 1051, 2129]

Other Studies. Serum hexosamine is increased in acute rheumatic fever but is no more specific than are more simple tests.[200] Complement activity was studied in rheumatic fever and was not significantly different from normal levels.[1106] [This is not in agreement with other reports.—Ed.] Serum glutamic oxalacetic transaminase was increased with greatest frequency in rheumatic fever patients with evidence of carditis, but was considered to have no merit as a useful test to determine rheumatic activity.[1542] [We agree—Ed.] Serum tocopherol levels were low in three cases of acute rheumatic fever, and increased with clinical improvement.[965] Vitamin A, serum carotene [2164] and serum phospholipids in rheumatic fever [2162, 2163] were discussed. Hemagglutination tests utilizing red blood cells sensitized to streptococci with rabbit antiserum [1923] and with periodate [1145] were described. Rheumatic fever sera gave slightly higher titers than did normal sera in these systems. The effect of histamine on circulating eosinophils did not differ from the normal in acute rheumatic fever patients tested.[1079] Urinary coproporphyrin was increased in children with acute rheumatic fever.[1525] The role of hemolysis in rheumatic fever was discussed.[1717] Skin tests employing the topical application of nicotinic acid [2124, 2125] and Trafuril [772, 1822] were investigated further. The absence of the normal hyperemic response correlated well with other evidence of rheumatic activity. [Others have failed to confirm this correlation.—Ed.] No evidence of abnormal ascorbic acid or tyrosine metabolism was found in metabolic studies of 24 young patients with active rheumatic carditis.[1666]

In one report, ballistocardiographic (BCG) analysis in 170 patients with acute rheumatic fever showed abnormalities in 80% of those with clinical carditis,[51] but another [6] concluded that most mild cases of acute rheumatic fever had normal BCGs even when unstable electrocardiographic abnormalities and changing heart murmurs indicated cardiac involvement.

Cardiac output studies in acute rheumatic fever patients demonstrated normal resting levels but an impaired exercise response.[158] The radiographic features of rheumatic pneumonitis were thought to be nonspecific.[745, 746]

Relationship to Other Diseases

Rheumatoid Arthritis. The relationship between rheumatic fever and rheumatoid arthritis remains unclear, as do questions relating to rheumatoid and rheumatic carditis.[1136, 2081] In 38 of 750 cases of rheumatoid arthritis, the onset was so acute as to suggest rheumatic fever; in fact, one patient developed carditis with mitral and aortic lesions; another died of congestive heart failure eight

months after onset of symptoms and development of joint deformities.[1136] Of 117 nonrheumatics in a series of 2,045 referrals for suspected rheumatic fever, five had rheumatoid arthritis; one, ulcerative colitis. Both rheumatic fever and rheumatoid arthritis may have similar eye lesions (scleritis and episcleritis, conjunctivitis, uveitis, iritis).[795] "The symptoms [of the two disorders] may be so similar that differentiation is impossible,"[1820] and "occasional borderline cases should make us wary of regarding them as separate entities."[1136] ["Borderline cases" usually turn out to have rheumatoid arthritis.—Ed.] Progression of joint changes to actual deformity has been called pathognomonic of rheumatoid arthritis.[1820]

Differential Diagnosis

The onset of rheumatoid arthritis may be so acute and migratory that it suggests rheumatic fever;[1167, 1820] so may that of lupus erythematosus, periarteritis and dermatomyositis.[346] A case of berylliosis has been reported where the initial findings suggested rheumatic fever.[1979] Anemias; heart disease other than rheumatic; various febrile and infectious states, including tuberculosis, brucellosis, infectious mononucleosis, nephritis, tonsillitis; central nervous system disorders; allergies and drug reactions; malnutrition, and various neurotic symptoms are some of the disorders which may be confused initially with rheumatic fever.[1400, 1820, 2181] Functional heart murmurs, "growing pains," nosebleeds, tics, "fidgets," fatigue and tachycardia are frequent occurrences, particularly in children, which may arouse suspicion of rheumatic fever.[346, 1463, 1820, 1878, 2181] The pains of rheumatic fever, unlike nonspecific, nonrheumatic pains in children, are characteristically present during the day, made worse by activity, and located in the joints proper. Failure of joint pains to respond to adequate levels of salicylates "almost surely" rules out rheumatic fever.[346] [We agree that the response is usual, and prefer the words "tends to."—Ed.]

Course, Prognosis and Results

In a 20-year follow-up of 1,000 original cases of rheumatic fever, 50% of 600 surviving patients were found to be leading normal lives.[1066] Erythema marginatum was considered to be of no prognostic value.[298] Follow-up studies[2190] of 110 children seven years after their attacks of scarlet fever revealed that, of the 10 children with electrocardiograms showing a prolonged conduction time during the acute illness, eight were thought to have definite or probable rheumatic heart disease; no heart disease was detected in those children without a prolonged conduction time during the acute illness. There was, however, no close follow-up during the intervening years to document the possibility of intercurrent streptococcal infection; a significant number of "nonrheumatics" had apical or pulmonic heart murmurs.

Etiology and Pathogenesis

Several general reviews of the pathogenesis of rheumatic fever appeared.[162, 415, 520, 864, 901, 1298, 1696, 2166] They considered the possible allergic basis for the disease, including the evidence incriminating hemolytic streptococci, and the effects of streptococcal toxins. Such other influences on the development of the

disease as heredity, nutrition, stress and endocrine activity were also discussed.[921] One unconfirmed report[1618] suggested that rheumatic fever is primarily an enzymatic disease, involving a deficiency in the hexose polysaccharide sulfate esters, followed by the production and accumulation of "heparinoid toxin"; this was thought to result in a deficiency of thromboplastin mechanisms. [There was little experimental evidence to support this position. A recent symposium summarizing the nature of rheumatic fever discusses treatment and prophylaxis of the disease.[314, 1389, 1487]—Ed.]

A group of 343 children were studied in Miami, Florida, during the spring of 1953:[1821] 16% had group A hemolytic streptococci at least once. No acute rheumatic fever or acute glomerulonephritis was observed in any of these children. It was shown[351] that delay for as long as nine days in the penicillin treatment of streptococcal throats in young adults was followed by a drop in the expected incidence of acute rheumatic fever, without influencing the usual rise in ASO titer.

Antibody responses in rheumatic and nonrheumatic patients continued to receive attention. One hundred twenty-one Schick-negative inactive rheumatics on no therapy were shown to have normal antitoxin responses to purified diphtheria toxoid.[1178] [These findings have since been confirmed and extended.[1676]—Ed.] One author stated[1872] that the lack of a high antistreptolysin titer excludes the possibility of rheumatic fever. A review of the immunologic aspects of rheumatic fever[752] covered the older literature and failed to distinguish between auto-immune, iso-immune and heterologous antibody responses. With gel-diffusion technics[902] it was shown that sera of patients with streptococcal infections had as many as seven different antibodies to streptococcal culture supernates. This study was similar to another,[869, 870] in which partially purified streptolysin "O" was used as the antigen.

Immunologic reactivity was studied by examining the levels of complete and incomplete antibodies after a single inoculation of *B. abortus* antigen in 42 rheumatic subjects and a control group.[2153] The rheumatic subjects developed normal and incomplete antibodies at a faster rate than did the normal subjects. These observations were interpreted as "giving further support to the hypothesis of the allergic origin of rheumatism."

Further attempts have been made to produce rheumatic-like lesions in the guinea pig[1064, 1065] and the rabbit:[1486, 1750] when connective tissue lesions were seen, they appeared to be nonspecific. Myocardial lesions which resulted from a single intrapharyngeal injection of group A streptococci were similar to those seen in lesions of human rheumatic carditis.[1486] Their appearance in the rabbit heart within 24 hours of induction of pharyngeal infection suggested that a nonimmunologic mechanism was involved. One unconfirmed report[1758] demonstrated complement-fixing antibodies in low titer to rat collagen in rabbits. Vascular and renal lesions were produced in rabbits[761] as a result of large dosages of bovine serum albumin. When Liquoid was used as the eliciting agent for Shwartzman's reaction, this reaction could be prevented[2085] by the previous administration of heparin. Striking myocardial necrosis was produced in laboratory animals by the intravenous injection of crystalline streptococcal proteinase[1113] and papain.[1114] [Whether the cardiac tissues of man are susceptible to the action of group A streptococcal proteinase remains to be determined.—Ed.]

A well documented review on the relation of hypersensitivity to rheumatic fever appeared.[16] One unconfirmed report[1719] indicated the presence of antibody in low

titer to saline extract of human myocardium among patients with rheumatic fever. An acid polysaccharide was recovered [109] from white blood cells of rheumatics, and proved to have certain similarities to a substance isolated from the liver of a patient with amyloid disease. Studies in rabbits showed that antibody to variants of the group-specific carbohydrates of streptococci produced on mouse passage showed considerable cross-reactivity.[1890]

In a study of nutritional factors in rheumatic disease,[1024] it was noted that the urinary excretion of vitamin C as well as the plasma level of vitamin A is decreased in rheumatic fever. This is similar to what may be expected in patients with pyrexias from other causes. In an uncontrolled study, it was suggested [1395] that rheumatic disorders may be related to vitamin C deficiencies.

In a group of papers appearing from a single laboratory [534, 537, 627, 628, 629, 1108, 1109, 1110] the relation of plasma 17-hydroxycorticosteroids to various aspects of rheumatic fever was reported. It was shown that in acute rheumatic fever there is an initial elevation of the 17-hydroxycorticosteroids, followed by a prolonged decrease below normal values. The circulating ACTH was often found to be greater than the normal value. Unlike normal subjects, rheumatic fever patients did not develop an increase in the plasma 17-hydroxycorticosteroids in association with salicylate intoxication. A "segmental adrenal insufficiency" in association with rheumatic fever was postulated. The urinary excretion pattern of 17-ketosteroids in acute rheumatic fever proved to be the same as in normal individuals.[1314] Corticotropin and corticosterone, in that order, were found to be less effective than was hydrocortisone in inhibiting antibody formation in rabbits.[1090] In a study of the antipyretic action of cortisone in rabbits, it was shown that it did not prevent the transient leukopenia which characteristically precedes the onset of fever, nor did it prevent the appearance of the "serum factor" associated with fever.[69]

Treatment

Rest. The value of rest in the treatment of acute rheumatic fever was again mentioned.[1404, 1681] It was felt that patients with obvious carditis should not be permitted to walk until all signs of clinical inflammation had subsided. In the absence of carditis, however, and after the clinical symptoms had disappeared, ambulation was permitted in spite of persistent laboratory abnormalities.[1681]

Salicylates. *Mode of Action.* A number of studies were done to test the hypothesis that salicylates act as antirheumatic agents by stimulating the endogenous production of corticotropin or by directly stimulating the adrenal glands, in either case increasing the secretion of adrenal cortical steroids.

Salicylic acid given subcutaneously to rats in doses of 300 to 500 mg./Kg. caused depletion of adrenal ascorbic acid.[400] Salicylamide in similar doses was given orally and intraperitoneally to rats, and a decrease of ascorbic acid and cholesterol in the adrenal gland was noted.[698] Salicylates in the treatment of patients with rheumatic fever had no effect on blood vitamin C levels.[21]

In one study the urinary excretion of adrenocortical steroids was normal in patients receiving large doses of sodium salicylates.[1944] Other workers [629] found that the mean excretion during salicylate therapy was slightly but significantly lower than in the pre-therapy and post-therapy periods. These same observers [1854] found the plasma 17-hydroxycorticosteroid level also to be low in rheumatic fever patients treated with salicylates; but others [124] noted no significant change in this level in patients similarly treated.

In acute experiments with normal human subjects, plasma salicylate peak levels over 27 mg.% were produced without causing any constant change in plasma 17-

hydroxycorticosteroids.[535] Although a markedly elevated circulating level of 17-hydroxycorticosteroids was found in 13 nonrheumatic patients,[536, 537] eight rheumatic patients with salicylism did not develop increased levels.[537] The observers postulated that salicylates may have increased the rate both of production and of utilization of adrenal steroids, with resulting essentially normal levels.[626, 630] This group also studied the response of the adrenal gland to stimulation with ACTH before and after treatment with salicylates. A decreased increment of 17-hydroxycorticosteroids after ACTH stimulation was observed in the post-therapy period. Since untreated rheumatics with activity for six months or longer showed no differences in responsiveness from that noted during the first two weeks of the disease, the decrease in responsiveness of the adrenal gland after salicylate therapy was not thought to be due to the natural course of the disease.[1855] [On the basis of studies done in one laboratory (J. J. B.), it was concluded that the antirheumatic effects of salicylates are not mediated through adrenal cortical stimulation.—Ed.]

Metabolism and Toxic Effects. Full therapeutic doses of aspirin in the treatment of acute rheumatic fever did not alter the high level of oxygen consumption associated with the untreated disease; the levels fell when the drug was withdrawn. The salicylate isomers, *para*-hydroxybenzoate and *meta*-hydroxybenzoate, were ineffective both clinically and in altering oxygen consumption.[395] Therapeutic concentrations of salicylate produced metabolic stimulation on mouse liver slices in a Warburg respirometer; higher levels caused decreased oxygen consumption.[1981]

Toxicity resulting from large doses of salicylates in children was again described.[986] Hyperpnea was the most common evidence of toxicity. A report emphasized the danger of sodium salicylate's precipitating congestive heart failure in rheumatic carditis.[1625]

Therapeutic Effects. Illingworth et al.[1004] observed for more than 30 months the course of unselected rheumatic children treated with bed-rest and nonsalicylate analgesics, and a comparable group treated with sodium salicylate in doses sufficient in most cases to maintain the plasma salicylate level above 30 mg.%. The salicylate group had a significantly quicker fall in temperature and in sedimentation rate. Fewer children in the salicylate group developed nodules; fewer suffered relapses or had recurrences of arthritis; fewer developed apical diastolic murmurs and, of those who did, more lost them; and more were apparently free from cardiac involvement at the time of the last examination. However, these latter differences were not statistically significant. [A longer period of follow-up is necessary before final evaluation of these data.—Ed.] Early and long treatment with salicylates was advised.[1681]

Steroids. Many papers were devoted to a comparison of the effects of steroids and salicylates.[538, 589, 594, 985, 990, 1082, 1404, 1421, 1681, 2030, 2061] The results of the Coöperative Clinical Trial of corticotropin, cortisone and aspirin by British and American groups[1421] have already been presented in the Eleventh Review. In summary, at the end of a one-year follow-up these workers found no significant difference among the three drugs in protecting the heart. However, in order to make the groups comparable, it was necessary to fix rigidly the dose and duration of therapy with each of these agents. Several other observers also noted no significant difference among patients treated with salicylates, cortisone or corticotropin,[990, 1082] but one group,[538, 944, 1107] using larger doses of corticotropin and cortisone, for longer periods of time, obtained better results with the steroids than with salicylates; and another[2030] obtained better results with cortisone than with corticotropin or salicylates. Such studies are extremely difficult to control, since none of these drugs is curative, and evaluation must be based entirely on suppressive effects.[544] [There is no good evidence as yet that

adrenocortical steroids prevent either cardiac damage during the acute attack or the late cardiac sequelae. Adequate doses of salicylates over adequate time periods provide satisfactory results in the majority of patients with rheumatic fever. However, steroids should be used early and in adequate dosages in patients with moderate or severe carditis accompanied by congestive failure, pericardial and/or pleural effusion, pulmonary congestion or edema. Short-term adrenocortical therapy (even for three or four months) does not carry the hazards of long-term therapy, as in rheumatoid arthritis. The final answer to this question will not be known for many years, and the difficulties in early diagnosis will make interpretation difficult even then.—Ed.]

Three factors were considered to be important in the possible prevention by the use of steroids of permanent cardiac damage.[834, 839, 938, 1168, 1352] To be of value, cortisone and corticotropin must be given in adequate dosage and for a sufficient period of time, and must be started sufficiently early in the course of the attack of rheumatic fever. Suggested adequate doses were one International Unit per pound per day for corticotropin,[538] and for cortisone 3 mg. per pound per day initially,[538] with 300 mg.[834, 1352, 1406] or even 400 to 500 mg. per day in severe cases.[1168] [Proper doses are undetermined, but will probably vary with the individual circumstances.—Ed.] It was felt that treatment should be continued at these levels until all symptoms had subsided and the laboratory tests had returned or were returning to normal;[538] other reports, however, recommended steroid therapy for six weeks arbitrarily.[1352, 1406] After this initial therapy, the doses were to be tapered slowly. In rheumatic fever the crucial time by which steroid therapy should be started if it was to be effective in preventing permanent cardiac damage was considered to be no more than one week,[1369] two weeks,[834] or three weeks.[1352] In a significant number of patients in some series,[480, 1406, 1421] rebound followed withdrawal of steroids. The well recognized steroid side-effects were again seen.[835, 1352] Combined steroid-salicylate therapy was recommended.[985]

During the period covered by this Review, many surveys of the value of cortisone or corticotropin in acute rheumatic fever and rheumatic carditis were published.[216, 594, 601, 721, 1066, 1369, 1370, 1832, 1977, 2064, 2170] Experiences gained in treating 83 patients in the protracted phase of rheumatic carditis with cortisone, ACTH and hydrocortisone were summarized by Taran and his associates.[2064] Hormone therapy produced symptomatic improvement in proportion to the degree of exudative manifestation before treatment. The therapeutic effects upon the insidious manifestation of the disease, i.e., the smoldering carditis, were classified as simple palliative, life-saving or unmasking effects which, in equivocal cases, helped to elucidate the nature of the disease. Of great concern were the 22 children with mild carditis who developed acute exudative manifestations during the course of hormone therapy or shortly after the therapy was discontinued. In these cases, hormone therapy was considered to have had an adverse influence upon the patient's defense mechanism against the disease.

The question of surgery in rheumatic heart disease is beyond the scope of this Review. A poorly controlled study was reported in which an attempt was made to reduce the large number of active, asymptomatic lesions observed from auricular appendage biopsy during mitral commissurotomy. Several patients were treated preoperatively with cortisone, and a decrease in the frequency of these lesions was noted.[774] The reactivation of rheumatic fever following surgery was discussed.[666]

The effect of cortisone upon the adrenal[411, 1208] and the pituitary glands[655] was reported. The influence of cortisone and corticotropin on the plasma electrophoretic

pattern[2131, 2132] and of corticotropin on exchangeable sodium content and body weight[15] was also studied. Intrapleural and intrapericardial hydrocortisone was used in the treatment of effusions in these areas.[92]

Other Drugs. In uncontrolled studies, phenylbutazone seemed to be of some value in the treatment of acute rheumatic fever.[1082, 1127] Vitamin C,[1395] and hyaluronidase given subcutaneously in the region of involved joints,[1758] and desensitization with minute doses of stock streptococcal extract[1930] were also used, but no definite conclusions could be drawn.

Prevention of Rheumatic Fever

Control of Streptococcal Infections. The importance of the control of group A hemolytic streptococcal infections as a practical means of preventing initial attacks of rheumatic fever was again emphasized.[102, 155, 156, 175, 259, 261, 296, 356, 501, 597, 598, 701, 1067, 1295, 1296, 1692, 1784, 2022, 2023, 2028, 2165] Various attempts that were made to modify the incidence of streptococcal infections by environmental control, tonsillectomy, immunization, sulfonamide prophylaxis and penicillin prophylaxis were reviewed.[501]

In a controlled study made during an epidemic involving personnel of a U. S. Air Force Training Base, it was found that an oral dose of 250,000 units of crystalline-buffered penicillin G twice daily for 10 days was an effective mass prophylactic against group A streptococci.[155, 156] The 10-day period appeared to be essential for an effective reduction in the streptococcal carrier rate. This treatment period could not be reduced even if the dosage was increased. Treatment for periods of five days had a much less suppressive effect on the carrier rate. No alteration in the penicillin sensitivity of the epidemic strains was noted. Similar results were reported in naval recruits.[598]

It was again pointed out that penicillin is the drug of choice in the treatment of streptococcal infections or for the eradication of the carrier state. To be effective, therapy must be continued until streptococci are completely eradicated from the throat.[2023] The schedules for use of the various forms of penicillin have been adequately covered in previous Reviews. Favorable reports were again made on the single intramuscular injection of 600,000 to 1,200,000 units of N,N^1-dibenzylethylene-diamine dipenicillin G (benzathine penicillin G—Bicillin).[1614] These dosages eradicated the infecting organism in 99% of 257 patients with exudative pharyngitis.[356] When treatment was started within the first week, there was inhibition of antistreptolysin formation, and no cases of suppurative complications or rheumatic fever occurred. In the smaller control group, two cases of acute rheumatic fever and one of acute nephritis developed. In a series of 1,175 children treated by a single dose of 600,000 units of benzathine penicillin G for β-hemolytic streptococcic infections, none developed rheumatic fever.[259] Ninety-four per cent of the children were cured of their infection. Of the clinical recurrences, 79% occurred one month or more after the initial treatment. An injection of 600,000 units of benzathine penicillin G should give low but effective blood levels against the β-hemolytic streptococci for from 12 to 14 days, while 1,200,000 units should result in detectable penicillin serum levels for from three to four weeks.[1668, 2027]

Prevention of Recurrence of Rheumatic Fever. It was stressed that the prevention of recurrences of rheumatic fever depends upon the protection of the

patient against infection with group A streptococci.[7, 577, 2025] An excellent outline of the methods and common drugs used for this purpose was given in the revised statement of the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association.[1067] It was recommended that, in general, prophylaxis should be continued throughout life. The dosages recommended were either sulfadiazine in the dosage of 1 gm. daily in the morning (0.5 gm. for children under 60 pounds); oral penicillin, 200,000 to 250,000 units once a day before breakfast; or intramuscular benzathine penicillin G, 1,200,000 units once a month.

The various methods were discussed.[2024, 2028] No recurrences of rheumatic fever were observed in 145 rheumatic subjects who received monthly injections of 1,200,000 units of benzathine penicillin G over a period of two years. Among 111 patients who received 200,000 units of penicillin daily by mouth, there were two recurrences of rheumatic fever. Five of 73 patients receiving 1.0 gm. of sulfadiazine daily had recurrences of rheumatic fever. Of those receiving benzathine penicillin G, cardiac lesions progressed in three patients, but in none did apparent rheumatic heart disease develop during prophylactic treatment. Reactions due to penicillin hypersensitivity were few and relatively mild. In another series,[514] 96 children with rheumatic fever were maintained on 1,200,000 units of repository benzathine penicillin G every four weeks for 14 months without evidence of recurrence. Similarly, no recurrences were reported in 46 patients with recent rheumatic fever given benzathine penicillin G injections of 1,200,000 units over an average period of 24 months.[1399] In a control group of 46 patients on sulfonamides, two clear-cut and four questionable recurrences occurred. The results were less favorable,[1351] however, in a study comparing oral benzathine penicillin in dosage of 200,000 units daily with sulfonamide in dosage of 0.5 to 1 gm. a day. Among 82 patients receiving the penicillin orally, four frank recurrences were observed, while five occurred among the 64 patients on sulfonamides. Of interest was the fact that detectable blood levels of penicillin were obtained in only 59% of samples taken six hours after the ingestion of the penicillin. In a total of some 450 patients, the effectiveness of a daily oral dose of 200,000 units of benzathine penicillin G in preventing the recurrence of rheumatic fever was reported.[644, 2094, 2095] [These studies were carefully controlled.—Ed.]

In one survey in New England,[1468] 34% of 245 patients treated at home admittedly failed to take adequate penicillin by mouth as prescribed for the control of acute beta hemolytic infections. Patients receiving medication without charge failed as frequently as those who paid for the drug. For those patients who develop streptococcal infections while on sulfonamide prophylaxis, one injection containing 600,000 units of aqueous procaine penicillin and 600,000 units of benzathine penicillin G was advocated.[102]

Other Drugs. Five hundred six patients [350] with streptococcal exudative pharyngitis were treated for periods of five days with oxytetracycline, each receiving a total of 10 gm. of the drug. A group of 480 patients who received no specific therapy served as controls. In the treated group, five patients developed rheumatic fever within 35 days as compared to 12 in the control group. Recurrent pharyngitis occurred more frequently in the treated group. The authors recommended that penicillin be the drug of choice in the treatment of streptococcal infections. Erythromycin, chlortetracycline and oxytetracycline should be reserved for those patients who are

unable to tolerate penicillin and, if employed, should be administered for at least 10 days.[867] [The gastrointestinal complications of these wide spectra antibiotics make prolonged use impractical. The cost also is prohibitive.—Ed.] Prompt initial clinical response with negative throat cultures resulted from doses of 800 mg. of erythromycin daily in patients suffering from streptococcal infections. However, in those patients treated for only three to five days, 45% had positive throat cultures for group A streptococci by the twenty-first day. In those receiving the drug for seven days, 13% were again positive by the twenty-first day. Aureomycin was used as a prophylactic agent in 28 rheumatic fever subjects in dosage of 10.4 mg./Kg. for periods of five to 35 months.[2188] There were no recurrences of rheumatic fever in this group, and the drug was well tolerated, with few side-effects. Only two of 223 throat cultures for β-hemolytic streptococci were positive.

Community Responsibility and Public Health Services. The total control and prevention of rheumatic fever through the treatment of streptococcal infections can be carried out effectively only when the full resources of the community's public health services are mobilized.[275, 2209] Community rheumatic fever programs require more than the diagnostic skills and treatment abilities of physicians to meet successfully the challenge of this long-term disease. Such comprehensive programs have brought public recognition of the importance of the total needs of the individual during the active disease, the necessity for uninterrupted prevention schedules and the value of optimal educational, vocational and social development opportunities. Three programs which attempted to explore this idea were described.[296, 1596, 2209] These involved extensive public and physician education, facilities for prompt diagnosis and reporting of streptococcal throat infections, and, in one community, free provision of penicillin for treatment and prophylaxis. [The effectiveness of these programs was difficult to judge since the number was relatively small, with no control groups in nonepidemic years. —Ed.]

Sydenham's Chorea

Although some authors maintain that chorea may occur without rheumatic fever,[1463, 1550] all agree that the occurrence of chorea must be taken as indicative of rheumatic fever "until proven otherwise";[1463] Cassels is unequivocal in emphasizing that choreiform movements, whether or not associated with systemic evidence of infection, are rheumatic in origin, and that chorea may be accompanied by other stigmata of rheumatic fever, either clinical or laboratory, but often is not.[346] Chorea must be differentiated from the normal "fidgetiness" of children, from tics, the neurologic manifestations of rheumatic fever complicated by subacute bacterial endocarditis and other diseases of the nervous system.[346, 1463, 2181] Chorea victims are almost exclusively in the five- to 15-year age group, and females are affected three times more frequently than males.[1550] Decreased concentrations of circulating adrenal steroids and elevated circulating corticotropin levels have been reported;[18] one case report and one uncontrolled study reported the favorable effects of hormone therapy.[19, 1550] Abnormal electroencephalograms were recorded in 14 of 20 patients with acute rheumatic fever in one series,[1543] and in six of 10 patients in another series.[1253] The relationship of Sydenham's chorea to infection with streptococci was studied,[2065] and 10 of 65 patients were found to have had a lag period of two months or longer after the onset of the acute rheumatic fever before the development of the chorea.

The longer after the attack the patients were observed, the less likely they were to have an elevated antibody titer to the streptococcal antigens.

Rheumatoid Arthritis

Clinical Manifestations of Rheumatoid Arthritis

The incidence of rheumatoid arthritis among patients with rheumatic symptoms was similar in office practice and in large clinics; of 200 patients with rheumatic complaints, more than one quarter (27.5%) had rheumatoid arthritis.[396] The sex ratio of females to males in rheumatoid arthritis varied considerably with the age of onset, being about 3:2 for ages from 15 to 50 years of age, 7:1 in the sixth decade, and about 1:1 after age 60.[1725] The onset of rheumatoid arthritis after the age of 50 is not infrequent, although often overlooked. Such onset was described in 23 patients;[2297] the disease process in this "elderly group" resembled that described in younger individuals.

Onset of Disease. The articular manifestations in 264 consecutive patients with rheumatoid arthritis were precipitated by trauma in 7%, acute hypersensitivity in 4%, acute infection in 11.5%, and severe emotional stress in 14.5%.[920, 921] The potential "triggering" effects of psychologic stresses were reëmphasized.[592] The onset and subsequent exacerbations of rheumatoid arthritis showed a seasonal distribution, with a greater frequency in winter and early spring, often corresponding to the prevalence of upper respiratory infection.[1725]

The variable, atypical modes of onset, and the lack of any test specific for rheumatoid arthritis, make the diagnosis of early rheumatoid disease difficult indeed.[1680] Morning stiffness, gradually improving with physical activity during the day, was one of the earliest and most consistent symptoms of rheumatoid arthritis.[391] Joint stiffness, while by no means specific, was such a constant complaint that prepared questions regarding this symptom might well provide a screening test for the disease.

Trauma was not thought to play a role in the development of rheumatoid arthritis; it may aggravate the disease already present in the joint traumatized.[1397] The relationship of surgical operations to the onset was subjected to an investigation in Finland.[1081] Thyroidectomy was found to precipitate the illness in two patients and to be responsible for its exacerbation in two others.

Articular Manifestations. Of 750 patients with rheumatoid arthritis, five experienced no pain for several years despite obvious progression of the disease and the absence of any neurologic disorder.[1136] Remarkable lack of pain was seen in a patient with marked bony resorption and the advanced deformities of the so-called "opera-glass" hand.[1373] It was suggested that absence of pain might be due to inflammatory destruction of pain and trophic fibers in the joint and periosteum.

Rheumatoid involvement of the temporomandibular joint was often associated with trismus, severe pain during mastication and/or subluxation of the articular surface of the condyle.[367] An apparent recession of the mandible was a characteristic deformity after prolonged involvement of the temporomandibular joints, particularly if this dated back to childhood, although ankylosis was rare.[1566] Factors in this deformity included involvement of the growth center of the condyle and hyperactivity of the depressor muscles of the mandible.

The clinical picture of rheumatoid arthritis of the cricoarytenoid joints was described in four cases with severe disease.[1471] In the acute stage the symptoms included fullness or tension in the throat, painful swallowing with occasional radiation of pain to the ears, hoarseness, and a local sensation of dryness or of a foreign body and dyspnea. In the chronic stage of cricoarytenoid arthritis, complete ankylosis produced a disabling dyspnea requiring tracheotomy. [Two cases of this bizarre, distressing manifestation have been encountered by one of us (D.C.G.).—Ed.]

Painful shoulder was experienced by 57% of 277 patients with rheumatoid arthritis.[1200] Rheumatoid disease, manifested by tendinitis and tenosynovitis, as well as by intra-articular disease, was the likely explanation of the shoulder pain in approximately one-half of the patients with shoulder symptoms. Affection of the sternoclavicular joint was described in four cases of rheumatoid arthritis.[1958] Systematic examination of this joint elicits tenderness in roughly one-half of the cases; it was emphasized that involvement occurs with greater frequency than is usually recognized clinically.

Extra-Articular Manifestations. *Skin.* Ulceration of the skin, chiefly of the lower extremities, was noted by several.[972, 1202, 2263] Cutaneous rheumatoid nodules with ulceration were observed in 12 of 2,000 patients with rheumatoid arthritis.[1202] Single or multiple, these ulcers, usually preceded by local edema, were torpid and resistant to therapy, especially during active disease. The absence of erythema following local application of nicotinic acid or its esters (niacin furfural, "Trafuril") was observed and regarded as a diagnostic aid by some;[932, 2124] the observation was not confirmed by others.[1236] No significant difference was found between the range of actual skin radiation pain thresholds in patients with rheumatoid arthritis and that in normal individuals.[127]

Tendons, Sheaths and Fascia. Compression of the median nerve in the volar carpal tunnel (carpal tunnel syndrome) was described in a patient with rheumatoid tenosynovitis of the flexor tendon sheaths.[842] Spontaneous rupture of extensor tendons of the fingers was observed in five patients with rheumatoid arthritis.[1201] Biopsy of the tendons in two patients revealed rheumatoid nodules. Attention was called to two types of heel lesions in 19 rheumatoid patients, with pathologic confirmation in four: one was a sub-Achilles bursitis which often eroded the os calcis and finally obliterated the bursa; the other was a soft-tissue erosion of the plantar surface of the os calcis.[313]

Cardiovascular Manifestations. Several instances of valvular heart disease, assumed to be rheumatic, were reported in patients with rheumatoid arthritis.[1238, 2081] However, the opinion was expressed that there is not yet sufficient evidence for concluding that any form of heart disease is diagnosed more frequently in living rheumatoid arthritics than in the general population.[1725] [We have the impression that, if cardiac involvement is sought for more carefully, clinical signs of carditis will be found more commonly than in the general population.—Ed.] Auscultatory, phonocardiographic, radiographic and electrocardiographic studies failed to reveal a higher incidence of abnormalities among 100 patients with rheumatoid arthritis than among 100 controls. However, a significant difference observed in hypoxemic tests was unexplained; positive results were more frequent in the rheumatoid group.[610] According to some observers, rheumatoid patients tended toward low arterial pressures;[2117, 2296] one author found these pressures to be higher than normal in a group of patients all under 50 years of age.[1032]

Pulmonary Manifestations. Pulmonary lesions simulating acute atypical pneumonia, acute rheumatic pneumonia and acute diffuse interstitial pulmonary fibrosis

were described in three patients with rheumatoid arthritis.[1790] In a single case report, transient inflammatory lesions of the lungs coincided with transient relapse of rheumatoid arthritis.[897] In a series of 253 patients with rheumatoid arthritis, the incidence of various nonspecific pulmonary lesions appeared to be higher than in a control series; however, no specific lung lesion or temporal correlation between the pulmonary disease and exacerbation of rheumatoid arthritis was observed.[59] An analysis of 24 reported cases and two new cases with respiratory manifestations of rheumatoid disease grouped seven cases as having pleural lesions, 14 as having diffuse parenchymal lesions and six as having pulmonary nodules.[1970] The coincidence of diffuse cystic lung disease and active rheumatoid arthritis was thought to be fortuitous.[914]

Other Manifestations. The iritis or uveitis seen in patients with rheumatoid arthritis was commonly classified as nongranulomatous, in contrast to the granulomatous type which is associated with sarcoidosis and such chronic infections as tuberculosis and toxoplasmosis.[145, 795] Reference was again made to scleral disease in rheumatoid arthritis: scleritis,[1567] scleral nodules[748] and scleromalacia perforans.[737, 1874]

Leukopenia and splenomegaly in association with rheumatoid arthritis (Felty's syndrome), with accompanying hypersplenism, were reviewed.[669, 689, 785, 1003, 2133] Splenectomy resulted in a prompt hematologic remission in four cases[669, 689, 1003, 2133] where cortisone and/or ACTH had failed to improve the condition. That hypersplenism is responsible for the blood changes in Felty's syndrome was supported by the reversion of the blood to normal in three patients after splenectomy.[621] [It should be clear that splenectomy in patients with rheumatoid arthritis and hypersplenism (Felty's syndrome) is not to be considered as treatment for the arthritis. Furthermore, neutropenia with granulocytopenia is not in itself a cogent indication for splenectomy. We believe that only when complications of neutropenia develop, such as repeated infections, ulcerations that do not heal or in some cases when definite hemolytic anemia develops, is splenectomy warranted.—Ed.]

In two of 15 arthritic patients with atrophy of the first interosseous muscle, the mean duration of the action-potentials evoked by contraction of the muscle was significantly less than normal.[1619] This was thought to be due to a myopathy, presumably rheumatoid.

Natural Course of Disease. With the introduction of more effective means of suppressing the signs and symptoms of rheumatoid arthritis has come an increasing awareness of the paucity of accurate information on the natural history of this disease and the factors which influence its course.[574, 1726] From the few long-term studies which have been conducted, it would appear that about 50% of patients fare reasonably well regardless of the treatment used. In 15 to 25% the prognosis is excellent. In the 50% who do badly, about 15% become inactive with residual disability and the remainder run a course of exacerbation and remission over many years, with only 10% being crippled.[574] Factors favoring a good prognosis include early disease, male sex and an insidious onset; a moderate or severe anemia combined with a rapid sedimentation rate usually implies a more unfavorable prognosis.

Difficulties encountered in studies of the course of rheumatoid arthritis were enumerated as: criteria for admission of patients to the follow-up series, choice of criteria for measuring the course, the collection of data and the methods of analysis.[1726] [More precise data on the course of rheumatoid arthritis are essential, for without such knowledge it is impossible to distinguish between the effects of therapy and the natural fluctuations of the disease process. The valuable contribu-

tion of Short, Bauer and Reynolds (Commonwealth Publishers, Boston, 1957) is an analysis of 293 rheumatoid patients studied over a period of 25 years. This monumental treatise will long stand as an important reference source concerning the natural course of this illness.—Ed.]

Diagnostic Criteria. Reports dealing with the diagnosis of rheumatoid arthritis ranged from a mere listing of the clinical features of the disease[517, 640, 2172] to helpful suggestions in early cases with an atypical onset and course simulating other musculoskeletal conditions.[574, 1435, 1786, 2196] Other diseases with joint symptoms simulating those of early rheumatoid arthritis include the shoulder-hand syndrome, hypertrophic pulmonary osteoarthropathy, gout, Reiter's syndrome, serum sickness, rheumatic fever and other collagen diseases.[574, 1031, 2196] [The criteria for the diagnosis of rheumatoid arthritis adopted by the American Rheumatism Association concisely define this disease.[1771] Their wide use is recommended.—Ed.]

On clinical grounds, and because of the absence of destructive residual changes, palindromic rheumatism was differentiated from rheumatoid arthritis.[1257] [The majority of the Committee favor the view that palindromic rheumatism usually represents an atypical or prodromal manifestation of rheumatoid arthritis. One co-author (J.J.B.) observed a patient who had classic palindromic rheumatism for four months and had a complete five-year remission following several injections of gold. He then developed typical rheumatoid arthritis with subcutaneous nodules and a high titer sheep cell agglutination and bentonite flocculation test. Another co-author (W.S.C.) followed three cases with this syndrome into typical systemic lupus erythematosus with renal involvement in all. The need for additional long-term studies is obvious.—Ed.]

Pathologic Characteristics

The concept that rheumatoid arthritis is a generalized connective tissue disease was given further credence by a number of studies.[160, 293, 410] Lesions of the joints, tendons and tendon sheaths, muscles, nerves and subcutaneous tissues were well documented; described, in addition, were widespread lesions in all stages of evolution and healing, and involving blood vessels, serous membranes, heart, lung, kidney and aorta.

Nodules. The histogenesis and morphology of various stages of development of subcutaneous rheumatoid nodules were reviewed.[293, 410, 2160] Histochemical studies indicated that active cellular synthetic processes, as well as degenerative and necrotizing processes, contributed to the formation of the nodule.[658] These lesions may progress to large cystlike spaces filled with degenerated, grumous, puslike material.[1135] Nodules were found in the pericardium, myocardium, endocardium, heart valves, visceral pleura, sclera and dura mater.[622, 1333] Therapy with cortisone (up to 13 months) caused softening and variable reduction in the size of subcutaneous nodules without significant alteration in microscopic structure.[2295] [Cortisone or related steroids in large doses may cause a reduction in the size of subcutaneous rheumatoid nodules but no appreciable effect when used in doses suitable for safe, long-term administration. Nodules may appear for the first time during steroid therapy.—Ed.]

Joints. A punch biopsy technic, simple and satisfactory for obtaining synovial tissue, was described.[1649] Synovial biopsy (by arthrotomy) studies of eight

patients with rheumatoid arthritis of seven days' to nine months' duration provided descriptions of the early phases of joint lesions.[1181] While there were marked variations in the same joint and from case to case, three main types of tissue reaction predominated: (a) generalized proliferative synovitis, confined to the surface layers in the earliest lesions. It was most marked in the portions of synovia adjacent to articular cartilage; (b) the deposition of fibrin or fibrin-like substances and necrobiosis accompanied a superimposed, more intense and localized tissue injury; and (c) focal or segmental vascular lesions, with inflammatory cell infiltrations and hyperplastic thickenings of the walls. The vasculitis was associated with both of the above lesions. It was thought that the relatively early articular lesions resembled the reactions characterizing the subcutaneous nodules and other systemic lesions of rheumatoid arthritis. [Specificity was not implied.—Ed.] The sternoclavicular articulation was found to be affected in a significantly high proportion of cases of rheumatoid arthritis, and is a structure readily accessible for routine autopsy study.[1958]

Bones. Massive resorption of bone simulated cysts and neoplasms in patients with rheumatoid arthritis.[636, 1373, 1907] Curetings showed pannus erosion by granulation tissue, with direct communication between the synovium and the cyst.

Cardiovascular System. Significant cardiac pathology was demonstrated in 38 of 43 adults with rheumatoid arthritis.[636] Uncomplicated arteriosclerotic heart disease was found in only three; the alterations also included granulomatous lesions resembling rheumatoid nodules, nonspecific myocarditis and pericarditis, valvular (predominantly aortic) changes and coronary angiitis. An aortitis, resulting in aortic regurgitation and occurring almost exclusively in males with rheumatoid spondylitis, showed structural features suggesting a rheumatoid origin.[89] This lesion, limited to the root of the aorta, showed a pannus-like thickening of the intima and deformity of the valve cusps. An associated inflammatory and destructive process involved the aortic wall. "Rheumatoid" nodules were observed in the myocardium and pericardium. [Approximately 50 cases of rheumatoid aortitis have been reported at the time of this review. Although almost all patients were males with rheumatoid spondylitis, exceptions have been noted. Two cases occurred in association with peripheral rheumatoid arthritis alone, and one patient was a female (W.S.C.).—Ed.]

All stages of the evolution and regression of necrotizing vasculitis were demonstrated in postmortem studies of two patients with "malignant rheumatoid disease."[160] The basic lesion was believed to be one of fibrinoid necrosis of the wall of small blood vessels. Coalescence of these injured vessels, and the inflammatory responses, resulted in a lesion indistinguishable from the nodule of rheumatic fever. It was suggested that these evolutionary rheumatoid lesions in the heart are often responsible for the pathologic lesions heretofore ascribed to rheumatic fever in patients with rheumatoid arthritis.

A subacute disseminated arteritis involving small arteries of muscular type was found in 18 of 72 autopsied patients with rheumatoid arthritis.[462] It was characterized by little or no necrosis of the vessel wall, adventitial lymphocytic infiltration, edema and histiocytic infiltration of the other coats, with subsequent fibrosis and, rarely, thrombosis. The lesions were found in the heart, peripheral nerves, skeletal muscle and synovium, but not in other viscera. More severe necrotizing vascular disease of the polyarteritis nodosa type was reported in five patients with rheumatoid arthritis.[91] Four of these patients had polyarteritis superimposed upon established rheumatoid

arthritis; the other developed the joint manifestations during the later stages of clinical polyarteritis. In the four cases mentioned above, the diagnosis of rheumatoid arthritis was clearly justified on clinical, radiologic and serologic grounds; histologically there was a typical rheumatoid process in the joints. In addition, disseminated arteritis lesions of the polyarteritis nodosa type were found in the periarticular tissues. Only one of the four cases had received cortisone; none had received ACTH. It was stated: "Though polyarteritis nodosa is a rare complication of rheumatoid arthritis, the association of these two conditions is more than coincidental."

[The occurrence of disseminated arteritis in rheumatoid patients treated with cortisone and allied steroids makes this report timely. Since Slocumb (1953) first drew attention to a panmesenchymal and panangiitic reaction with the use of withdrawal of cortisone, many reports have described instances where the lesions of polyarteritis nodosa developed during

TABLE 2

Occurrence of Amyloid in Rheumatoid Arthritis

Biopsy of		Amyloid Positive			Amyloid Negative		
		+	+?		−?	−	
Metatarsophalangeal joints	26	14	8	22	1	3	4
Lymph nodes	7	4	2	6	—	1	1
Hygromata, bursae (in the feet)	23	9	4	13	3	7	10
Rheumatic nodules	26	9	6	15	3	8	11
Appendix	5	3	—	3	—	2	2
Nodules, bursae (in calcaneal region)	16	3	3	6	4	6	10
Synovia	46	15	5	20	8	18	26
Tendon nodules	41	5	9	14	6	21	27
Skin	65	15	8	23	4	38	42
Other tissues	34	6	10	16	2	16	18
Total	289	83	55	138	31	120	151
Per cent	100	28.7	19.0	47.7	10.8	41.5	52.3

and following the period of administration of the hormone. It is clear from a report by Ball [91] that a similar sequence of events may arise in the absence of ACTH or cortisone therapy. In a recent paper by Kemper, J. W., Baggenstoss, A. H., and Slocumb, C. H. (Ann. Int. Med. **46**: 831 (May) 1957), the conclusion is reached that cortisone definitely increases the frequency of polyarteritis in rheumatoid arthritis. We agree that this complication is increased by steroid therapy.—Ed.]

Other Visceral Lesions. Pulmonary lesions were described in three patients with rheumatoid arthritis.[370] These included pleural fibrosis of diffuse and nodular type, localized areas of fibrinous pneumonia, and hyalinized and necrotic collagenous scars in interstitial tissue and lung parenchyma. In another report, alterations in connective tissue deposits in the lung were ascribed to an associated rheumatoid arthritis.[822] [This careful pathologic study attempts to distinguish the modified pneumoconiosis in Welsh coal miners with rheumatoid arthritis from the changes in orthodox pneumoconiosis. It is an excellent review of the recently described syndrome (Caplan's syndrome) of nodular lung fibrosis associated with rheumatoid arthritis.—Ed.] Tissue responses, somewhat similar to those of the rheumatoid nodule, were found in the pneumoconiotic lesions of coal miners. While some of the described changes might have been related to disease entities which coexisted with rheumatoid arthritis, such as pulmonary tuberculosis and pneumoconiosis, it appeared to some that degeneration of pulmonary connective tissue was more prominent in the presence of rheumatoid arthritis.[822, 1441] Others commented that, if this was true, its occurrence must be extremely rare.[1629]

Of 45 autopsied cases of rheumatoid arthritis, amyloidosis was present in 11 (24%), with renal amyloidosis the cause of death in nine (20%).[753] There were several other illustrations of amyloidosis in rheumatoid arthritis.[383, 659, 1013, 1150, 1194, 1708, 1806, 2073] A series of 289 biopsies and surgical specimens from patients with rheumatoid arthritis revealed amyloid deposits in 83 (28.7%); in 55 specimens (19%) the findings were less distinctly positive (table 2).[1199] An enhancing effect of cortisone and ACTH on the experimental production of amyloid deposits was noted.[1606]

Histologic studies of hepatic tissue obtained from patients with rheumatoid arthritis revealed only minor alterations in two of 15 available specimens.[1232] There was complete lack of correlation between clinical and laboratory evidence of hepatic involvement and the histologic appearance of the liver.

Laboratory Studies in Rheumatoid Arthritis

Electrolyte Studies. The mean value of potassium in the serum of 50 patients with rheumatoid arthritis was significantly higher than in a control group of a comparable size—21.7 mg.% as compared with 19.0 mg.%. The difference in the serum sodium content in this same series of patients was not statistically significant.[1080]

The presence of osteoporosis in typical rheumatoid arthritis prompted a reinvestigation of the serum calcium and phosphorus concentrations and urinary excretions of these substances.[983] In 10 patients given intravenous calcium gluconate infusions, the results corresponded to values obtained from normal subjects. The observers concluded that there was no connection between this disease and parathyroid function.

Hematologic Studies. Certain characteristics of the anemia of rheumatoid arthritis were reported. The primary defect in the majority of patients was felt to be failure of the marrow to produce normal numbers of red blood cells,[582] together with some shortening of the red-cell life span in a few patients.[583] Significant hypoferremia with normal iron-binding capacity was observed,[582, 1789] while absorption of iron from the gut was normal.[1037, 1789] A significant increase in plasma volume in about 20% of patients was noted,[527] but the hematocrit was thought to be a valid index of the anemia despite the hemodilution.[582] A parallel was drawn between the anemia of rheumatoid arthritis and that of infection, with elevation of free erythrocyte protoporphyrin and serum copper often found in both types.[1038] Although the concentration of intravenously injected saccharated oxide of iron dropped abnormally fast in rhumatoid patients, there was some disagreement as to whether the intravenous administration of iron was of any therapeutic value.[582, 583, 1037, 1038] After extensive investigations of anemia in this disease, one group concluded: "Of the various forms of therapy for the anemia of rheumatoid arthritis, only cortisone appeared to have any definite effect. Iron therapy, either oral or intravenous, and blood transfusions are not of proven benefit." [Transfusions often help, but steroids are effective in almost all cases.—Ed.] That hypersplenism is responsible for the blood changes in Felty's syndrome was supported by the reversion of the blood to normal in three patients after splenectomy.[621] Iron, vitamin B_{12}, folic acid, hormones and blood had given only temporary benefit, but splenectomy arrested the blood dyscrasia.

Sedimentation Rate. Direct correlations were noted between the erythrocyte sedimentation rate and the plasma specific gravity,[579] and between the sedimentation

rate and the level of plasma fibrinogen.[482] Sedimentation rate methods were again compared, and the Westergren was considered to be superior to the Wintrobe because of better approximation of the "Rouleaux formation intensity" of the plasma, due to the dilution of the blood by citrate solution.[1251] A three- to 20-year follow-up of 21 patients showing elevated sedimentation rates in the absence of disease was reported.[1269, 1557]

Serum Proteins. Qualitative and quantitative alterations of serum proteins and associated carbohydrates were of continuing interest. Increase of the gamma globulins in active rheumatoid arthritis was again confirmed[409] and was said to occur at some time after increase of alpha globulins.[1770] The increases in globulins and carbohydrate-like materials, as measured by paper electrophoresis, were believed to be proportional to the magnitude of the inflammatory response. It was suggested that response to therapy could be evaluated by following the return of these fractions toward normal.[1179] In other studies, the polysaccharide components associated with the globulins, measured chemically, were found to be increased in some patients, presumably as a manifestation of the inflammatory process.[78, 79, 200, 837, 1387] The polysaccharide: protein ratio was proposed as an objective measure of the degree of inflammation.[1593] A colorimetric test for probably abnormal serum mucoprotein complexes was of no greater diagnostic value than the sedimentation rate.[354, 660]

A new term, "dysprotidaemic joint disease," was used for a case having clinical characteristics of rheumatoid arthritis with laboratory findings of a plasmacytomatosis. This and other cases described by Chiti, where a plasma cell reaction is an outstanding feature, have deposits of an anomalous protein in articular tissues.[739]

The serum diphenylamine reaction has been reported to be increased in rheumatic fever. In one study this test was found to compare favorably with the sedimentation rate in reflecting the clinical activity of rheumatoid arthritis.[354] However, in another investigation,[660] of patients with clinically active rheumatoid arthritis but with normal erythrocyte sedimentation rate, the diphenylamine reaction was not of much value as an indication of activity.

Synovial Fluid. The first electrophoretic analysis of normal synovial fluid was reported.[1640] A component migrating between albumin and hyaluronic acid was noted and given the designation "π component." The proteins of synovial fluid and serum of patients with rheumatoid arthritis were compared, and it was suggested that the synovial membrane's power of selective permeability was lost as the magnitude of the disease process increased.[1610] The synovial fluid protein pattern became progressively more like that of serum with the duration of the effusion. A rapid C-reactive protein method was applied to synovial fluid from patients with rheumatoid arthritis, rheumatoid spondylitis and gonococcal arthritis, and to effusions from osteoarthritis and arthritis due to trauma. The acute phase protein was absent in effusions of traumatic origin, while it was present in the former conditions; this difference was thought to have distinct diagnostic importance.[337] The disappearance of the acute phase protein,[337] as well as other changes in the synovial fluid toward normal,[1755] was noted after administration of adrenocortical steroids. Fletcher[695] examined the viscosity of synovial fluids from 32 patients with rheumatoid arthritis and 20 patients with osteoarthritis. Limiting viscosity and anomalous viscosity measurements indicated no essential difference in the mean degree of polymerization of hyaluronic acid in the two conditions.

Roentgenograms. Attention was again called to subarticular bony cysts demonstrated radiologically in patients with rheumatoid arthritis.[464] Of five

patients with massive bony resorption, three had rheumatoid arthritis.[1907] Three characteristic radiographic features were described: in the first, the small bones of the hands and feet were involved, with resulting telescoping of phalanges, the so-called "opera-glass hand"; in the second, the long bones were involved, with small and large osteolytic, cystlike lesions; and in the third, there was tapering and disappearance of large portions of the distal parts of the long bones.

Serologic Tests. Several variants of hemagglutination tests were reported, and superior specificity and/or increased sensitivity was claimed for each.[26, 210, 734, 1405, 2154] Human O cells sensitized with rabbit anti-O-cell antibodies[1630] and sheep red cells coated with human plasma Fraction II (gamma globulin),[939] as well as human O cells simply treated with periodate,[1145] were found to be agglutinated by most rheumatoid sera. The use of the euglobulin fraction, rather than whole serum in a direct agglutination, was said to lead to enhanced specificity; so was an indirect, rather complicated inhibition technic.[2291] Separation of the agglutination factor from serum by dilution of the serum in cold distilled water was said to increase the specificity of the reaction.[2044, 2045]

The bewildering number of modifications of the agglutination procedure made difficult the estimation of the specificity of the agglutinating factor. In one review,[1629] positive reactions varied from 35% to 89% of cases, depending upon the agglutination method used. The coexistence of pneumoconiosis and rheumatoid arthritis resulted in a higher incidence of positive agglutination tests than did the arthritis alone.[90] [Progress in the development of a reliable and sensitive serologic test for rheumatoid arthritis is most encouraging. Many centers are concentrating on this problem, and practical technics are now under extensive clinical trial. A conference on Serological Reactions in Rheumatoid Arthritis was held in 1957. A summary of the proceedings of this conference prepared by Dr. R. W. Lamont-Havers is available upon request to the Arthritis and Rheumatism Foundation, 10 Columbus Circle, New York 19, N. Y.—Ed.]

Other Tests. In addition to the sedimentation rate, other nonspecific tests for inflammation included the demonstration of the intravascular aggregation phenomenon[1195] and the determination of the serum C-reactive protein.[1887] The serum precipitation test of Jokinen was found to have no diagnostic significance.[984] Varying degrees of activity of the enzyme plasmin (fibrinolysin) and its inhibitor, antiplasmin, were found in rheumatoid sera.[880, 881] A more consistent finding in this plasmin-antiplasmin proteolytic system was reported by Thomas.[2082] In 43 patients with rheumatoid arthritis the levels of serum antiplasmin were increased and varied with the severity of the disease. In these same patients the plasmin levels were reduced but were unrelated to the state of the disease as expressed by the sedimentation rate. Hepatic functional tests in patients with rheumatoid arthritis gave results which were inconclusive.[1197, 1198, 1758] Of 13 patients with active rheumatoid arthritis, abnormal electroencephalograms were obtained in seven, with evidence of focal activity in three.[1253] Cerebrospinal fluid abnormalities were present in four, while seven subjects showed abnormal psychometric tests. There were no significant clinical neurologic findings.

Etiology and Pathogenesis of Rheumatoid Arthritis

An excellent review described the significant data and promising current research on the etiology and pathogenesis of rheumatoid arthritis.[555]

Factor of Heredity. The importance of genetic factors in diseases of later life was reëmphasized.[2287] On the basis of previous calculations (Eleventh Rheumatism

Review),[1] it was reiterated that 1.16% of the population have the "proper genetic constitution" for rheumatoid arthritis, and one-half of these, or 0.58%, are affected.[1991] One family with vertical inheritance through three generations was reported.[1988] A woman and her grandmother had the disease, but the second generation was not involved. The need for case reports of familial occurrence was stressed, since the principles of genetics depend upon knowledge of such pedigrees.

Factor of Hypersensitivity. The phenomena manifested in sensitized erythrocyte agglutination tests in rheumatoid arthritis were the subject of major investigation (see Laboratory Studies, this section). Such tests were of vital interest, not only because of their usefulness in clinical diagnosis, but also for their possible contribution to an understanding of the basic morbid process, uninfluenced by changes in the inflammatory state.[555] The substance or substances (rheumatoid factor) responsible for these positive agglutination reactions were found to be variously associated with beta globulin,[1746] with gamma globulin,[1206] and with Fraction III.[940] The substance was dissimilar from thermostable fourth component of complement (C'4),[2149] and it could be separated from rheumatoid serum by ethanol fractionation, with resultant partial chemical characterization.[940] A material having the same agglutinating activity was produced by culturing nonhemolytic cocci on tissue containing collagen.[2044] Materials agglutinating sensitized sheep cells and those agglutinating streptococci were compared and found to be distinct serum factors.[1206, 1568, 2092] No striking alteration of the complementary activity of blood could be detected.[1106]

[Several studies of the agglutinating (rheumatoid) factor are in progress. The increasing volume of research in this field suggests the importance of this lead, but reproducible results will await application of more refined methods of protein chemistry and immunochemistry. The excellent work of Kunkel and associates,[710] utilizing ultracentrifugal methods in characterizing one of the "rheumatoid factors," is a step in this direction.—Ed.]

Skin testing of 20 patients with rheumatoid arthritis and 20 controls was performed to demonstrate possible incorporation of bacterial antigens, or sessile antibodies to such antigens, on the surface of rheumatoid tissues.[1215] The lack of any local or systemic response in either group to a variety of rheumatoid extracts, introduced intradermally, led the authors to conclude that "those features of rheumatoid arthritis which suggest infection or chronic allergy, or both, may not be mediated by the standard serologic reactions which involve antigen and antibodies."

The eosinopenic response to histamine was not significantly different in 49 rheumatoid arthritics and 51 controls.[1079] In a purely speculative paper, it was presumed that tuberculin-type allergy to beta-streptococcus is a principal factor in the relapse of rheumatoid arthritis, but sensitization occurs in time against the body's own proteins, and that various structures (i.e., joints, periarticular tissue, heart, etc.) are affected through an unknown "mediator," having an affinity for a specific tissue.[864]

In a study of the immunologic response of 2,500 cases of typical rheumatoid arthritis it was concluded: "It appears almost necessary to consider the pathogenesis of this disease in a view of a detrimental interplay of multiple infections."[2206]

Factor of Altered Metabolism. No evidence was obtained to support the concept of a specific relationship between joint tissue and plasma gamma globulin in rheumatoid arthritis.[2137] Neither normal nor rheumatoid subjects, nor their independently studied joint tissues in vitro or in vivo, differentiated between normal and rheumatoid I-131 labeled Fraction II (gamma globulin). It was observed, however, that the elimination from the circulation of injected proteins [I-131 tagged Fraction II (gamma globulin) and similarly tagged Fraction V (albumin)] was more rapid in rheumatoid patients than in normal subjects. The significance of this finding was undetermined.

Resistance exercises performed by two patients with active rheumatoid arthritis resulted in a protein anabolic effect in both as measured by mineral and nitrogen balance studies.[376] Identical effects were noted in one patient during the administra-

tion of testosterone. Exercise did not alter the excretion of 17-ketosteroids in the single patient on whom such determinations were made. Another careful metabolic study appeared to show that addition of an incomplete protein (gelatin) to the otherwise low-protein diet of a patient with rheumatoid arthritis could restore nitrogen equilibrium. In this study no differences were noted in vitamin C metabolism or in electrolyte balances in rheumatoid and control subjects.[1054]

Radioactive phosphorus employed for studying the activity of phosphorylizing enzymes in rheumatoid arthritis showed a higher level of phosphorus in the connective tissue of patients with rheumatoid arthritis, suggesting an aberration in phosphorylizing processes of carbohydrate metabolism.[1291] A study of the plasma lipids again revealed normal values, unaltered by usual doses of cortisone.[1116] A schema was presented purporting to relate the pathogenesis of rheumatoid arthritis (and all rheumatic diseases) to an intrinsic error in the biogenesis and metabolism of hexose polysaccharide sulfate esters (heparin).[1618] [More data will be necessary to support such a theory—Ed.] The excessive fall of serum glycine after the administration of sodium benzoate suggested a reduction in available glycine in patients with rheumatoid arthritis.[1242] These observations were consistent with previously reported disturbances of glycine metabolism in rheumatoid patients (Eleventh Rheumatism Review).[1]

Factor of Endocrine Imbalance. Much interest continued in the possible relationship of rheumatoid arthritis to dysfunction of the adrenal cortex.[584, 819, 1002, 2090] However, studies of possible qualitative or quantitative abnormalities in endogenous adrenocortical steroids again failed to reveal a specific metabolic defect.[50, 176, 177]

In only five of 16 rheumatoid patients did the oral administration of Compound S result in the expected normal increase in 17-ketosteroid excretion; this failure of response was not related to severity, duration or extent of the disease.[564] Subsequent tests (eight to 12 months later) in six patients suggested some correlation between clinical improvement and a higher urinary excretion of 17-ketosteroids following the administration of Compound S in three of these patients. [At present, abnormalities of adrenocortical function cannot be incriminated in the pathogenesis of rheumatoid arthritis. There is still much to be learned, however.—Ed.] Of 28 thyroidectomized patients, 18 allegedly experienced the onset or relapse of rheumatoid arthritis following surgery.[1196] Such a sequence was noted in only eight of 97 rheumatoids subjected to other major surgical procedures.

Factor of Autonomic Imbalance. Reference was made to the tendency among rheumatoid arthritics toward hypotension, and to the fact that certain antihypertensive agents, specifically hydralizine (Apresoline) and hexamethonium, can cause syndromes closely resembling several of the rheumatic diseases.[2117] Frequently, an acute or chronic emotional stress is linked to the onset of exacerbation of "the two nearly mutually exclusive disease processes, hypertension and rheumatoid arthritis." From all this comes a hypothesis that the precipitating factor in these diseases may be a hypothalamic disturbance resulting in abnormal efferent neural discharges which, in hypertensive patients with drug-induced antonomic blockage, are diverted into those pathways which result in the production of "collagen diseases" instead of hypertension. [Why these rheumatic syndromes occur in such a relatively small number (7.5%) of patients whose blood pressure is normalized with these drugs is not discussed.—Ed.]

Seven patients who had a good clinical response to cortisone showed a marked increase in the resting blood flow to the digits and a greater quantitative response to the reactive hyperemia test.[352] This effect did not occur in one cortisone-treated patient previously subjected to cervicothoracic sympathectomy, suggesting that "the peripheral vascular effect of cortisone may, like nor-epinephrine, depend on the integrity of the sympathetic nervous system, as well as on the patency of the peripheral vessels."

Psychogenic Factors. A thoroughgoing evaluation of all the literature on the

psychosocial factors in rheumatoid arthritis was presented, discussing in detail personality characteristics and conflicts, social background factors, psychologic mechanisms, and the similarity in personality structure of schizophrenics and rheumatoid arthritics.[1141] A new entity, "pre-rheumatic neurosis," beginning years before development of clinical rheumatoid arthritis and including an "avital-sanguine" temperament, repressed aggressivity, and severe narcissism, was described.[1662] Some "psychologic abnormality detectable and acceptable to a general physician" was believed to occur in 68% of 264 rheumatoid arthritic patients.[920, 921]

A study was made of the personality patterns and unconscious fantasies of 25 young white male veterans having rheumatoid arthritis; 20 patients with low back pain were used as controls.[381] The unique personality of the arthritic was that of an unusually overtly calm person who rarely expressed, or consciously felt, anger. Covertly, however, he contained hostile feelings. Aiding him in his defense against hostile expression was a unique body image, resulting from parental influences. As expressed through his Rorschach fantasies, the rheumatoid thought of his body as "a kind of hollow container filled with uncontrolled fluid material and surrounded by a hard, impenetrable surface." He attached unusual significance to his body and was unconsciously desirous of exhibiting it, though he denied his exhibitionist tendencies and, in fact, complained of his inadequacy and shyness.

Relationship Between Rheumatoid Arthritis and Other Diseases

Other Connective Tissue Diseases. Rheumatoid arthritis, polyarteritis nodosa, dermatomyositis, scleroderma, lupus erythematosus disseminatus and rheumatic fever are frequently grouped together because of widespread and common changes in connective tissue characterized by edema, fibrinoid, cellular infiltration, and vascular and fibroblastic proliferation.[320] The term "collagen diseases" had been originally proposed for this group when "collagen" was used in a broad sense to include all connective tissue components. As the definition of collagen has been narrowed to mean a specific fibrous component only, the broader term, "connective tissue disease," is increasingly used. Many clinical as well as pathologic similarities exist between members of this group of diseases.[91, 320, 2160] Whether the similarities are due to a limited capacity of connective tissue to respond to various stimuli or to a common pathogenic agent remains unknown. Until the latter is established, however, it was again agreed that these diseases should be regarded as distinct disease entities.

Considerable interest was aroused by the occurrence in rheumatoid arthritis of disseminated arteritis, L.E. cells, and false-positive serologic tests for syphilis, coincident with the therapeutic use of cortisone.[636, 1248, 1927, 2200] The possible relationship between the administration of corticoids and the evolution of a "panmesenchymal and panangiitic reaction" was suggested, but not established. [Since attention was first called to this relationship by Slocumb in 1953, there have been an increasing number of reports of periarteritis nodosa-type lesions proved by autopsy and biopsy in steroid-treated subjects. It must be noted that varying degrees of arteritis and even necrotizing arteritis have occurred in rheumatoid arthritis in the absence of treatment with oral corticoids or with corticotropin (see Pathologic Characteristics, this Section). The degree, then, to which steroids may actually influence the pathogenesis and severity of these lesions warrants further investigation. Several of us believe that the incidence of clinical polyarteritis has increased since the advent of corticosteroid therapy.—Ed.]

Freyberg et al. studied 80 patients considered to have rheumatoid arthritis with complications or an atypical form of this disease, and found that 25% had typical L.E. cells in the blood.[1396] In another study of 46 patients with rheumatoid arthritis, five showed typical L.E. cells and three had "tart cells" in the peripheral blood.[2194] [The question of the specificity of the L.E. cell in establishing the diagnosis of disseminated lupus erythematosus is an unsettled question. Experienced clinicians report positive L.E. cell tests in from 3 to 15% of patients having untreated rheumatoid arthritis and in a greater percentage of those treated with cortisone. If all patients who show the L.E. cell phenomenon have lupus erythematosus, then many established concepts concerning this illness must be changed. Since more benign cases of lupus erythematosus are now being diagnosed as the result of the L.E. cell test and a higher index of clinical suspicion, there is less dissimilarity between lupus and rheumatoid arthritis in joint manifestations, duration and prognosis than was formerly supposed.—Ed.]

Other Diseases. An association between psoriasis and rheumatoid arthritis seemed well established. Of 424 patients with rheumatoid arthritis, 4.2% had psoriasis; the incidence was the same in men and in women.[841] In most instances, the joint disease in these patients could not be distinguished from that of rheumatoid arthritis. The two most characteristic clinical features were the high incidence of bone destruction and the high frequency of psoriasis of the nails. The latter was not necessarily associated with arthritis of the corresponding terminal interphalangeal joints.

Increasing interest was shown in the common coexistence of rheumatoid arthritis and Sjögren's syndrome (keratoconjunctivitis sicca, rhinostomatopharyngolaryngitis sicca, and enlargement of parotid glands).[336, 440, 578, 611, 852, 1328] The frequent occurrence of rheumatoid arthritis was also reported in patients with Mikulicz's disease of unknown etiology (chronic enlargement of salivary and/or lacrimal glands), which was shown to be closely related to the sicca syndrome.[1477] Remission of the joint symptoms in a patient suffering from rheumatoid arthritis associated with Sjögren's syndrome occurred following an attack of mumps; two additional cases with infectious parotitis and arthritis, but without the sicca syndrome, experienced a complete joint remission.[1754] Lansbury described the twenty-eighth case of arthritis mutilans to be reported since this condition was first described by Marie and Leri in 1913.[1760] This case was unusual because of the coexistence of the "sicca syndrome" of Sjögren.

There appeared to be an antagonism between psychosis and rheumatoid arthritis in individual patients.[1141, 2110] A review of 9,000 admissions to a predominantly neuropsychiatric hospital disclosed only one patient with concurrence of these two clinical entities. [One of us (E. E. R.) is of the opinion that patients with rheumatoid arthritis are about as liable to psychoses as anyone else.—Ed.]

In a series of 45 autopsies on patients with rheumatoid arthritis, the causes of death and their incidence were listed as follows: infections, 31%; renal disease, 24%; cardiac disease, 22%; pulmonary embolism, 2%; cancer, 2%; miscellaneous, 18%.[753] Notable for their absence or infrequency were cerebral vascular accident, gastrointestinal disease, accidental death, pulmonary embolism, cancer and hypertensive heart disease. In comparison with other, similar investigations, this revealed a higher frequency of renal disease, of which amyloidosis was the most common cause (20%). [These results are quite different from the reported deaths in rheumatoid arthritis patients in the various steroid-treated series where deaths are attributed to polyarteritis nodosa or to hemorrhage or perforation of peptic ulcer.—Ed.]

A remarkably high incidence of patients with rheumatoid arthritis (95%) were found to be infected with *Entameba histolytica*. Approximately 30% of normal persons living in Oregon were clinically infected with this organism.[1737] [Either the incidence of amoebiasis in this disease is inordinately high in Oregon or investigators in other areas are less skilled in the recognition of this parasite. Since this report was published no confirmatory reports have appeared.—Ed.]

Juvenile Rheumatoid Arthritis

In a survey by the Division of Services for Crippled Children of Illinois the incidence of rheumatoid arthritis was found to be approximately 1% in 30,000 crippled children.[1682] Reports of 72 patients[736] and of 21 patients[1055] reviewed variations in the onset, clinical findings, and the course of juvenile rheumatoid arthritis. Erythematous maculopapular or morbilliform rashes of the trunk and extremities were frequent, occurring in 25%[736] and in 70%,[1055] but were often migratory and of short duration. In some patients, a skin rash preceded the initial joint symptoms by several months.[1055] Typical erythema marginatum was observed in four patients. [This strongly suggests rheumatic fever.—Ed.] Subcutaneous nodules occurred in six.[736] Bilateral ocular lesions were frequent in juvenile patients with rheumatoid arthritis. Band-shaped corneal opacities which were considered almost pathognomonic, plus chronic iridocyclitis or cataract formation, occurred in about 20% of patients reported in the literature.[818]

The large joints (knees and ankles) were usually initially involved in young patients, but later in the disease any joint in the body could be affected, with the exception of the dorsolumbar and sacro-iliac joints of the spine.[1055] However, in another series of patients with typical juvenile rheumatoid arthritis, clinical or radiographic evidence of spondylitis was present in 57 of 71 patients (80%); there was radiographic evidence of involvement of the cervical spine in 45 patients, and of the lumbar spine and sacro-iliac joints in 24 and 25 patients, respectively. The radiographic diagnosis of spondylitis in children with peripheral rheumatoid arthritis was distinguished from "congenital failure of segmentation" and also from the adult type of Marie-Strümpell arthritis. An outstanding feature of the spinal arthritis in this group of children was the lack of calcification of the paravertebral ligaments. Flexion deformity of the neck and a shortened stature frequently resulted from interference of the arthritic process with normal spinal growth.[99] [This valuable report emphasized the importance of careful observation and radiographic study to determine the incidence of spondylitis. However, one of us (B.M.N.) was able to demonstrate spinal involvement in only 16 and sacro-iliac changes in only five of 62 children studied for periods of from seven to 20 years.—Ed.] Interference with bone growth may produce cervical vertebral fusion, shortening of one or more fingers (brachydactylia) and failure of mandibular growth resulting in the production of a birdlike facies (brachygnathia). One fourth of the patients may show the last-named abnormality.[1055] Dentine dysplasia in a 14 year old girl with rheumatoid arthritis who had received high doses of vitamin D was attributed to hypervitaminosis D in early childhood.[226]

Great difficulty occurred in the differential diagnosis of juvenile rheumatoid arthritis from rheumatic fever, and in some patients from tuberculosis, leukemia, polyarteritis or disseminated lupus erythematosus.[519, 736, 1055, 1833] A normal antistrep-

tolysin-O titer (A.S.O. below 250 units) or a leukocytosis of over 20,000 per cubic millimeter was considered to be more characteristic of rheumatoid arthritis than of rheumatic fever.[1055] The serum antistreptococcal antibody titers may be useful in the differentiation of juvenile rheumatoid arthritis from rheumatic fever; the titers of antistreptococcal antibodies are usually lower in the serum of rheumatoid arthritics. [The A.S.O. titer may be very high in rheumatoid arthritis—Ed.]

The Sheep Cell Agglutination Test. There is a substance in the serum of adult patients with rheumatoid arthritis (the rheumatoid factor) which has the capacity to agglutinate sensitized particulate bodies (sheep erythrocytes, latex and bentonite particles). The percentage of positive agglutination tests is distinctly smaller in patients with the juvenile form of this disease. [Ziff [2289] summarized the results of 69 reported cases of juvenile rheumatoid arthritis with 26 positive tests (38%). Of 20 patients in his own clinic, all gave a positive test when the sheep cell inhibition procedure was used. He suggested that the low incidence of positive tests in juvenile disease might be attributable to the lack of sensitivity of the procedure employed, rather than to absence of the rheumatoid factor. A multiplicity of technics aimed at enhancing the specificity and sensitivity of this reaction are currently under investigation, and the future value of this test will depend upon these studies. This agglutination reaction is also discussed in the section on Laboratory Studies in Rheumatoid Arthritis.—Ed.]

Transient synovitis of the hip joint, a not infrequent entity in children and one which follows a benign, self-limited course, usually offered no difficulty in differential diagnosis because of the lack of involvement of other joints and the presence of swelling of the surrounding muscles, the swelling of the hip joint capsule, and the usually rapid subsidence of the process in a few days.[952]

The duration of activity of juvenile rheumatoid arthritis varied from a few months to several years; recurrences were not infrequent. Prognosis for complete or "functional" recovery was favorable in from 40 to 65% of cases.[736, 1055] [The prognosis in this disease was unfavorably influenced by prolonged duration of activity and by an acute onset with severe systemic symptoms. One of us (B. M. N.), in a study of 62 patients, observed that 77% made a good functional recovery, 18% were handicapped, and 5% had died.—Ed.]

Although it was generally accepted that there is no specific curative treatment for juvenile rheumatoid arthritis, and that results are often discouraging, most observers agreed that various drugs have a certain value in helping to control symptoms and prevent deformities.[519, 736, 1055, 1682] Many therapeutic measures were reported, including a basic program of bed-rest, salicylates, para-aminobenzoic acid, physiotherapy, splints, psychotherapy and chrysotherapy. Other therapy consisted of vitamin D2, tonsillectomy, steroid hormones or corticotropin, isoniazid, phenylbutazone (Butazolidin) and chloroquine.[519, 736, 1055, 1682, 1736, 1983] Eight of 11 juvenile patients (nine with amebiasis) had remarkable improvement from amebicidal therapy, including chloroquine, 500 mg. daily for several weeks.[1736] [The association of juvenile rheumatoid arthritis and amebiasis is rare in our experience. The results obtained by one of us in seven of 12 children given 125 to 250 mg. of chloroquine daily showed improvement when other therapy had been unsatisfactory. Further trial of the antimalarial drugs is indicated. See section on Rheumatoid Arthritis.—Ed.]

Treatment of Rheumatoid Arthritis

General Principles and Evaluation. A new awareness of the need for additional knowledge of the behavior and prognosis in rheumatoid arthritis in the absence of definitive treatment was expressed.[1473] "Rarely in the treatment

of disease has there been a greater need for clear thinking, accurate diagnosis and careful evaluation of therapeutic measures than is now the case in this disease."[1780] Without information of the natural history of this chronic disease, the practicing physician is unable to evaluate critically proposed specific or palliative methods of therapy. To place the study of the natural history of rheumatoid arthritis (and, as a corollary to this, the evaluation of therapy) on a sound level, three needs were apparent to one writer: a simple specific diagnostic test, uniform diagnostic criteria, and a method for evaluating progression of the disease.[1680]

The difficulty in diagnosing this complex disease, of which the cause is unknown and for which there are no reliable diagnostic tests which will differentiate it from other ill defined but closely related syndromes of the connective tissues, makes evaluation of therapeutic measures extremely problematic.[396, 963, 1680, 1762, 1786] A more intelligent appraisal of rheumatoid arthritis has resulted from controlled studies which have contributed much information about the natural course of the disease in untreated patients and in patients treated with only a fundamental program, not utilizing the "newer, so-called miracle drugs."[517, 572, 575, 1680] [More data on similar long-term studies are needed. The problem of assessing end results adequately is one of the most baffling. Newer methods based on objective measurements are currently being investigated. Until more reliable technics are developed, alertness to inconsistencies in claims of remedies for this disease must be maintained.—Ed.]

With advances in our understanding of rheumatoid arthritis has come the concept of "management" rather than "cure" or "treatment."[1680] A conservative program of management recommended bed-rest in the early, acute states, followed by a graduated program of activity; optimistic psychotherapy and a sympathetic relationship between the physician and patient; the patient's understanding the disease and the purpose of long-range therapy; improvement of general health by measures such as adequate diet, vitamins, transfusions, removal of infected foci, and all other required treatment; and the avoidance of steroids or phenylbutazone at the onset of therapy. It was considered most important to relieve the rheumatoid patients of worries about economic instability, the dread of crippling deformity, and social or family deprivations.[358, 396, 517, 572, 575, 639, 888, 963, 1436, 1535, 1680, 1762, 1786, 2172] Difficulties in accurate evaluation of analgesic drugs and the use of various technics were reviewed.[114, 134] [The measures enumerated here, plus salicylates in adequate doses, the regular use of suitable forms of local heat, daily practice of controlled and supervised exercises, postural instruction and appropriate measures to prevent deformities, including splints, constitute what has been termed the "basic program of treatment." Reliance on drugs rather than on these basic measures is an all too common tendency among doctors as well as patients.—Ed.]

Patient Orientation. It was agreed that an important part of successful management is to obtain the coöperation of the patient to the fullest possible extent. This requires an early, detailed explanation of the nature and course of rheumatoid arthritis and the necessity for a broad attack over a period of time, with emphasis on the fact that no miracles can be expected. The patient should be told that, although there is no "sure cure," there *is* hope, and that much can be done to prevent crippling and to arrest the disease. The patient's confidence

can be strengthened by an attitude of sensible, aggressive, open-minded, honest optimism on the part of the physician.[396, 963, 1762, 2172]

Rest and Motion

The importance of rest, both physical and emotional, was again emphasized. In early, severe rheumatoid arthritis, complete bed-rest was necessary; but it was also essential to maintain good posture with a firm mattress, bedboard, footboard or sandbags arranged to prevent deformities of the lower extremities. Muscle setting exercises and passive motion were carried out during this period to prevent muscle wasting, loss of joint mobility, or contractures. In some patients, application of plaster splints, to the knees and wrists especially, hastened the subsidence both of acute joint inflammation and of the general systemic reaction, and prevented flexion deformities of these important joints. In the less severely involved patients, a period of daytime rest plus adequate sleep at night was essential. A program of graduated active exercise was begun as soon as the signs of acute inflammation had subsided. [It is important to start bed exercises as soon as the patient is seen, regardless of signs of inflammation.—Ed.] The use of heat and massage relieved pain and muscle spasm. Excessive activity during the early stages of acute joint inflammation was harmful.[358, 396, 517, 639, 963, 1118, 1128, 1436, 1535, 1786] Such a fundamental program of treatment, including hospital care during the acute stage of rheumatoid arthritis (average stay of nine to 10 weeks), resulted in diminished activity of the disease, substantial increase in function of the involved joints, and improvement maintained as long as two years after discharge in 282 of 307 patients (70.5%).[572, 575]

[It is important when a "new" therapeutic agent is evaluated to assess results not only by considering the number of patients improved but also by comparing the duration of improvement with that produced by the basic, fundamental program of treatment described above.—Ed.]

Analgesics

Salicylates. Salicylates continued to be the analgesic drug of choice because of their low toxicity in the usual dosage of 3 to 6 gm. daily.[396, 517, 639, 1120, 1436] Dosage sufficient to maintain a blood salicylate level of about 15 mg.%, or just below toxic levels, was suggested.[572, 575, 639] [We agree.—Ed.] Gastric intolerance was not infrequent in rheumatoid patients (51 of 200 patients),[718] and occurred in 110 of 318 nonrheumatoid patients with peptic ulcers.[1495] Acute erosive gastritis with bleeding was observed frequently in the ulcer patients; aspirin was believed to be a major factor in at least one of every eight patients admitted to the hospital with hematemesis.[1495] Of 25 patients intolerant of plain aspirin, 24 tolerated buffered aspirin in a dosage of eight tablets daily administered for many months.[718] [This point needs further study.—Ed.] Salicylates were observed to deplete the adrenal ascorbic acid in rats;[1620] they increased glycogen disappearance from liver slices in certain media;[1943] and they accentuated the eosinopenic response to corticotropin in doses of 100 to 125 mg./Kg. of body weight, but not in smaller doses.[1548] A direct respiratory stimulant effect on the medulla, and also a profound metabolic effect with increased oxygen consumption due to action on skeletal and probably on cardiac muscle, were described.[2076]

Various combinations of salicylates with other drugs (para-aminobenzoic acid, sodium cinnamate, calcium succinate, and dexedrine) were reported to produce superior analgesia with less toxicity, presumably because of synergistic effects.[98, 280,

[305, 668, 783, 883] Salicylamide in combination with mephenesin and ascorbic acid was said to be more effective and better tolerated than salicylates,[1514] but salicylamide alone was found in a controlled study to be an ineffective analgesic drug.[114] Local inunction of 10% diethylamine salicylate cream was believed to relieve soft tissue rheumatic pain.[994] [No definite evidence has been presented that any of the reported combinations have antirheumatic activity, or that they have analgesic properties superior to those of the salicylates alone.—Ed.]

Phenylbutazone. Phenylbutazone (Butazolidin) has been employed in the United States since 1951 because of its analgesic, anti-inflammatory antipyretic properties in the treatment of many arthritic disorders. Although the mechanism of action was not known, phenylbutazone produced subjective and also objective improvement within a few days or a week.[267, 293]

Pharmacology. Phenylbutazone was found to be absorbed rapidly and completely from the gastrointestinal tract, with peak plasma levels in two hours. Oral dosage of 400 to 600 mg. daily produced a stable plasma level of 10 to 15 mg.% in three to four days. Intramuscular injection of 1 gm. resulted in slower absorption, with peak plasma levels in six to 10 hours. The drug was almost completely metabolized in the body.[164, 267, 277, 293, 1120, 1603, 2104] Metabolism occurred at a rate of 20% per day, and two metabolites identified in the urine represented only 3 and 5%, respectively, of the administered dose. One metabolite (hydroxylation of one of the benzene rings in the para position) was unusually stable and accumulated in the body in considerable amounts; apparently this compound was responsible for the antirheumatic and toxic effects of phenylbutazone. It was believed that the catalysts responsible for oxidizing phenylbutazone were present in the liver microsomes.[299, 300] The phenylbutazone formula was highly specific; only one derivative was found with a better anti-inflammatory index in animals.[120] From studies based on the determination of phenlybutazone in the plasma, it was demonstrated that three weeks were required for elimination; only traces were present in erythrocytes.[1488] Caution was advised with the use of the drug because of the azoprotein linkage (similar to aminopyrine), which could be the antigenic stimulus for leukocyte depression.[477]

Physiologic Effects. The metabolic effects of phenylbutazone, especially on sodium, chloride and water retention, and the hazards of administering this drug to elder patients with cardiac or renal impairment, were emphasized.[164, 267, 293, 485, 486, 518, 737, 1120] In two patients on a dose of 400 to 600 mg. daily, phenylbutazone was reported to have antithyroid activity. Studies suggested that organic binding of iodine was prevented. One patient developed a goiter, which disappeared when the drug was discontinued.[1478] A single oral dose of phenylbutazone increased gastric acidity in both dogs and humans in about 50% of the tests. A single intramuscular injection had no effect on gastric acidity in dogs, but prolonged injections produced gastroduodenal erosions and ulcerations.[1146, 1147]

Clinical Response. While both subjective and objective improvement of rheumatoid arthritis resulted, opinions differed considerably on the advisability of phenylbutazone therapy in this disease. All agreed, however, with its use in acute gouty arthritis; in acute shoulder syndromes or acute periarticular involvement or other joint arease, where dramatic results were frequently produced with only a few days of treatment; and probably in rheumatoid spondylitis, since patients with this condition responded better and suffered fewer toxic effects than did patients with peripheral rheumatoid arthritis.[54, 485, 486, 975, 1327, 1535, 1680, 2102, 2104] Many believed that the value of phenylbutazone in rheumatoid arthritis was not finally established because there was no evidence that

it retarded the pathologic process and because of its potentially serious toxicity.[293, 689, 713, 1381, 1680, 2155] However, a few expressed the opinion that the drug had not only analgesic but also antirheumatic action. Complete remissions were not uncommon,[485, 1120, 1126] and in 53 of 68 trials there was a decrease in the serum protein-polysaccharide ratio in rheumatoid patients.[1594]

Improvement occurred in 25% to 90% of rheumatoid patients treated for short periods of a few weeks to three months.[164, 277, 293, 499, 707, 1120, 1327, 1603, 2257] When the American Rheumatism Association classification was reported, 81 of 111 patients (73%) [499] and 85% of 255 patients (of 1,008 patients reviewed) [293] were improved by phenylbutazone therapy. It was suggested that the rheumatoid patient was refractory to phenylbutazone at certain periods; if the drug were discontinued for a few weeks and then re-administered, probably 90% of patients would eventually improve.[1120] [If patients with rheumatoid arthritis are not definitely relieved within two weeks on 300 to 400 mg. of phenylbutazone daily, the drug should be discontinued.—Ed.] The few reports of long-term administration did not clarify the question of prolonged benefit to rheumatoid patients from phenylbutazone. While one group of 147 (150 original patients) [900] had sustained improvement for periods up to 18 months, only 25% and 30% of 145 patients improved in the "stage of the disease," and in "functional ability" respectively during the same period of drug administration. [Objective improvement due to this drug has not been definitely proved.—Ed.] [485] In another group, only six of 29 patients had continued improvement after from three to six months of treatment.[2105]

Dosage of Phenylbutazone. Although considerable difference of opinion was expressed as to the optimal dosage schedule and the route of administration, it was recommended in most reports that initial oral doses should not exceed 400 to 600 mg. daily, and that reduction to 100 to 200 mg. daily should be accomplished as soon as warranted by the patient's response.[54, 277, 293, 499, 1120, 1478, 2102, 2257] Intramuscular injections (because of slower absorption),[164] or oral dosage omitting one or more days of the week,[485, 900, 1603] was believed to produce less toxicity. An adequate blood level (5 to 10 mg.%) of phenylbutazone was considered to be essential by some,[164, 277, 1120, 1488] but was apparently regarded by the majority as not related to the clinical response. The frequency of toxic reactions increased from 30% of patients at 5 to 9 mg.% blood concentration to 85% at 10 to 14 mg.%.[277] However, Pemberton [1603] believed there was no correlation between the blood level and toxicity, though only 36.5% of his patients had reactions with a 400 mg. daily dose, while 75% had reactions with a 1,200 mg. dose.

Toxic Reactions to Phenylbutazone. The incidence of toxic reactions continued to be high (from 25% to 60%).[54, 164, 277, 293, 485, 499, 707, 713, 1120, 1381, 1603, 2102, 2104, 2155, 2257] A review of the literature showed reactions reported in 32% of 1,594 patients,[2104] and also in 32% of 2,301 patients; [293] in another series of 3,934 patients, 1,199 (34.6%) had 1,543 different reactions.[1381] The most frequent reactions were gastrointestinal disturbances (30%); fluid retention (19%); dermatitis (14%); hematologic disturbances (11%); and exacerbations or bleeding of peptic ulcers (3%). These accounted for 77% of all reactions due to phenylbutazone.[293] In a comprehensive review of the reported toxic effects, 23 deaths were reported, 12 due to hematologic reactions (10 agranulocytosis), three to peptic ulcers with hemorrhage; two to renal failure, three to exfoliative dermatitis, and one to hepatitis; two were unclassified.[1381] [This was the probable total of deaths, although it was impossible to estimate the number of fatalities where the drug may have been a contributing factor.—Ed.]

In the majority of patients, toxicity occurred within four to eight weeks from the onset of therapy.[52, 54, 133, 277, 293, 366, 408, 481, 485, 499, 637, 639, 665, 753, 900, 1048, 1120, 1280, 1322, 1381, 1535, 1603, 1844, 1995, 1998] However, reactions such as renal failure,[224, 277] purpura and peptic ulcer[499] occurred as long as two years after the beginning of phenylbutazone therapy. In 12 of 48 patients, severe reactions justified discontinuation of drug therapy.[54, 267, 277, 293, 485, 499, 707, 713, 1120, 1327, 1594, 1603, 2257] Toxicity was minimized by the careful selection of patients, careful observation for the first weeks of therapy, and use of safe dosage schedules. Also, immediate discontinuation of the drug was found to eliminate practically all serious reactions.[849, 1120, 1603] Phenylbutazone was reported to be contraindicated in elderly patients, in patients with cardiac, hepatic or renal disease, and in patients with an allergic background, peptic ulcers, hypertension and hematologic dyscrasias.[164, 485, 518, 900, 1120, 1147, 1995, 2104, 2257] A 73 year old woman with rheumatoid arthritis and osteoarthritis tolerated daily doses varying from 200 to 500 mg. for 14 months without untoward effects.[954]

Gastrointestinal reactions (nausea, abdominal discomfort, bowel disturbance, and the activation and perforation of or bleeding from peptic ulcers) were the most frequently reported toxicities.[54, 133, 267, 277, 366, 408, 485, 499, 518, 639, 713, 975, 1120, 1147, 1327, 1512, 1535, 2105, 2257] Jaundice developed in six women, in two of whom phenylbutazone probably contributed to a fatal result.[637] Liver involvement was also present in patients with a fatal generalized "hypersensitivity reaction."[713, 1322, 1381] In a few patients with hepatic damage, complete recovery occurred.[133, 868, 1512, 1844] However, no hepatotoxic effects of the drug were observed with single doses in 11 cirrhotic patients, or with continued administration in four cirrhotic patients where a 10 mg.% plasma level was maintained for five months.[2187]

Edema due to sodium and water retention was a problem in many patients.[54, 164, 267, 277, 293, 485, 1120, 1535, 2102] Circulatory complications, such as cardiac decompensation or hypertension,[485, 1120, 1535] myocardial infarction[2257] and acute renal failure, were reported and caused several deaths.[224, 267, 277, 639, 1048, 1120, 1280] Hematuria was not infrequent.[707, 975, 1327, 2102, 2257] One patient apparently formed uric acid calculi with bilateral ureteral obstruction and anuria. This patient died after pulmonary embolism and coronary infarction.[2191]

Hematologic complications were the most serious and also the most unpredictable toxic reactions. Thrombocytopenia and agranulocytosis[52, 408, 477, 485, 639, 665, 707, 900, 1120, 1327, 1381, 1535, 1995, 1998, 2251, 2257] occurred, usually within the first few weeks of therapy, but were observed after 18 to 24 months of phenylbutazone.[499] At least 12 deaths from agranulocytosis, thrombocytopenia and aplastic or hemolytic anemia were reported in the literature;[1381] however, Gsell[849] believed that phenylbutazone was not a dangerous drug if carefully administered, because hematologic complications were infrequent in his experience in Europe.

Drug rashes (erythematous, morbilliform, erythema multiforme type, or urticarial), often associated with fever, were reported in 14% of 2,301 patients;[293] stomatitis with ulcerations was also a frequent complication.[54, 267, 277, 408, 485, 637, 639, 707, 755, 900, 1120, 1327, 2257] Hypersensitivity reactions resulting in at least five deaths were manifested by dermatitis, stomatitis, fever, granulocytopenia, jaundice, edema and other systemic findings, including polyneuritis, lymphadenopathy, myocarditis, septicemia, hepatitis or gastrointestinal bleeding.[133, 421, 713, 1322, 1381, 1512, 1545, 1844, 1995, 2171] Aptyalism was observed in a few patients;[485, 2171] other miscellaneous reactions, such as vertigo, lethargy or fractures of the femoral neck due to increased activity, were reported.[293, 485]

[Phenylbutazone is of limited value in the treatment of peripheral rheumatoid arthritis. It is worth a carefully supervised trial for from 10 days to two weeks in doses up to 400 mg. per day. If definite relief is obtained, the dose should be decreased to the minimal amount capable of maintaining symptomatic relief. Some of the co-editors seriously question

the advisability of prolonged phenylbutazone administration and do not use it, since there is no evidence that it influences the actual activity or progression of the disease.—Ed.]

Other Analgesics. The use of pregnenolone methyl ether in 15 patients produced marked subjective improvement in their sense of well-being, ability to relax, and ability to sleep without sedation.[396] There was no evidence of any abnormality in salt and water balance, carbohydrate metabolism or disturbance of the menstrual cycle. It was claimed to be useful in combating the tension and depression associated with rheumatoid arthritis. Histamine injections resulted in local and systemic relief in 65 patients with rheumatic disorders, especially in those with nonarticular diseases.[1612] [This was a poorly controlled observation, presenting no convincing evidence that histamine injections had any consistent beneficial effect on rheumatoid arthritis.—Ed.] Extensive periarticular (and also intracapsular) infiltration with Xylocaine was effective in 200 rheumatic patients.[1161] Dipyrone(a pyrazolone derivative), combined with salicylate, succinate and vitamin C, was an effective analgesic but of very limited value in arthritic diseases.[2136] Animal studies indicated that ethionine[120] had some anti-inflammatory activity and that some derivatives of hydroxycinchophen or phenylbutazone might have such activity because of the adrenal ascorbic acid depletion effect in rats.[1620] [None of the clinical data indicates any superiority to analgesic actions of the salicylates.—Ed.]

Cortisone, Hydrocortisone, Newer Steroids and Corticotropin in Rheumatoid Arthritis

The effectiveness as well as the limitations of certain corticosteroids and of corticotropin in controlling the manifestations of rheumatoid arthritis was reaffirmed.[32, 126, 213, 215, 216, 279, 289, 290, 292, 387, 432, 433, 571, 590, 638, 685, 721, 768, 888, 918, 955, 975, 1001, 1036, 1375, 1581, 1681, 1787, 1823, 1858, 1972, 1978, 1986, 2061, 2101, 2111, 2170, 2205, 2244] It became clear that the signs and symptoms of rheumatoid disability could be altered, and that, by the development of various synthetic steroids, desirable and undesirable properties of these agents could, to a degree, be dissociated.[944] Hormone therapy was not considered to be indicated in all cases of rheumatoid arthritis,[122, 208, 571, 1972, 1973] and its effectiveness was found to relate to proper selection of cases and appropriate dosage levels.[432, 2170]

New Synthetic Steroids. Synthetic steroids possessing biologic activity greater than that of the naturally occurring secretory products of the adrenal cortex became available for physiologic studies and clinical trials.[708, 724, 747, 804, 805, 1266, 1533, 1665, 2091] Substitution of a halogen for the 9 alpha hydrogen of either cortisone or hydrocortisone resulted in a group of steroids which were found to enhance in varying degrees the glucocorticoid, mineralocorticoid and anti-inflammatory activity.[227, 724, 725] The introduction of a double bond between the carbons 1 and 2 in the A ring of cortisone or hydrocortisone produced two new steroids (prednisone and prednisolone) with potent glucocorticoid and anti-inflammatory properties, but without increased mineralocorticoid effect.[980, 1611] Moreover, substitution of the 9 alpha hydrogen of the latter two steroids by a halogen further increased their carbohydrate and anti-inflammatory potency.[565, 1984]

The following synthetic steroids were shown to have greater carbohydrate activity than did equal amounts of cortisone: 9 alpha-chlorohydrocortisone acetate, 9 alpha-chlorocortisone acetate,[978] 9 alpha-fluorohydrocortisone and 9 alphafluoro-

cortisone acetate. Other less potent synthetic corticosteroids assayed for carbohydrate potency included 9 alpha-iodohydrocortisone acetate, 9 alpha-bromohydrocortisone acetate, 9 alpha-bromocortisone acetate, 9 alpha-hydroxyhydrocortisone acetate, 9 alpha-methoxyhydrocortisone acetate and 9 alpha-ethoxyhydrocortisone acetate.[724]

The preparation 9 alpha-fluoro-17-hydroxycorticosterone 21 acetate was assigned the term "fludrocortisone acetate" by the Council on Pharmacy of the American Medical Association.[42] It was found to be effective in the life maintenance of adrenalectomized dogs,[2050, 2051] and to have toxic effects similar to those of desoxycorticosterone in the rat.[1864] Anti-inflammatory effects of fludrocortisone and cortisone were compared by a cotton-pellet implantation technic in rats which indicated a potency ratio of 7.3:1.[565] The administration of fludrocortisone to humans resulted in eosinopenia;[747, 804] suppression of adrenocortical function as measured by urinary steroids;[747, 804, 882, 1721, 2202] loss of nitrogen, calcium and phosphorus,[882] and marked retention of sodium and water.[211, 747, 804, 882, 2168, 2169] This steroid proved to be a potent antirheumatic agent, but with limited therapeutic value because of excessive salt and water retention associated with its use.[42, 211, 214, 636, 882, 2154, 2168, 2169] In clinical trials, the antirheumatic potency of fludrocortisone was estimated to be 10 times that of hydrocortisone free alcohol.[211, 214]

The striking antirheumatic effects of prednisone and prednisolone were first reported by Bunim, Pechet and Bollet in 1955 [294] and subsequently described in detail. In patients given doses ranging from 30 to 60 mg. per day [generally therapeutically excessive.—Ed.], marked subjective improvement occurred, objective manifestations decreased, and the erythrocyte sedimentation rate and C-reactive protein became normal. Subsidence of the inflammatory process was also demonstrable by synovial biopsy. Prednisone was estimated to be two to five times more potent, milligram for milligram, than was cortisone or hydrocortisone without a proportionate increase in side-effects.[294, 399, 498, 541, 830, 913, 1349, 1456, 1776, 1974, 1975, 2143] [Subsequent long-term studies have indicated that, except for electrolyte changes, a proportionate increase in these analogues has the capacity to produce the same side-effects.—Ed.] Physiologic effects of prednisone and prednisolone were similar to those of other glucocorticoids, and included occasional hyperglycemia and glycosuria,[219, 291, 399, 498, 541, 636, 1508, 2091, 2143] reduction of the number of circulating eosinophils,[291, 294, 1776, 1975, 2091, 2143] suppression of urinary 17-ketosteroids [291, 294, 1508, 2143] and 17 hydroxycorticosteroids,[498, 1508] correction of adrenocortical insufficiency [294, 498, 1508] and increased excretion of nitrogen.[291, 294, 636, 2091] Sodium and water retention and increased potassium excretion were not observed during the administration of therapeutically effective doses of prednisone.[294, 498, 1974, 1975, 2091, 2143] With larger doses, however, electrolyte effects were apparent.[636, 1508, 2091] In general, alterations of serum electrolytes, proteins and cholesterol, and hemopoietic effects, were qualitatively similar to those previously observed during the administration of cortisone.[291, 294, 399, 2143]

Aldosterone, a naturally occurring adrenal mineralocorticoid isolated and identified almost simultaneously by Reichstein et al.[1912] and Mattox et al.[1878] became available for brief clinical use. No significant effects of aldosterone on the manifestations of rheumatoid arthritis were observed in several therapeutic trials.[2167, 2168, 2169]

Pregnenolone methyl ether administered orally had no beneficial effects on the arthritis in five patients to whom it was administered.[803] All five cases experienced moderate to marked temporary euphoria and an increased feeling of well being

associated with a reduction of the severe fatigue so often seen in patients with rheumatoid arthritis.

Pituitary-Adrenal Physiology. It was postulated from experimental data that in the biosynthesis of hydrocortisone and corticosterone, cholesterol is derived from two-carbon fragments and converted to Δ^5-pregnenolone by a split in the side chain at carbon 20, influenced by corticotropin. Δ^5-pregnenolone is then converted to active steroids by a series of enzymatic reactions independent of corticotropin.[935, 1479, 1632]

In studies of the nature of corticotropin, hormone activity of polypeptide hydrolysates of anterior pituitary extracts was again observed.[528, 1479] Active preparations having molecular weights of 5,000 to 6,000 and containing 14 or 15 amino acids were described.[1479] When corticotropin was infused intravenously in man, a rapid rise of 17-hydroxysteroids occurred. Steroid levels increased during the period of infusion, and maximal levels were achieved with a dosage of one unit per hour. When corticotropin gels were administered, steroid levels reached maximum in one to two hours and had returned to normal in six hours.[123] Higher plasma levels appeared in older patients.[2119] Excretion of ascorbic acid increased during the administration of corticotropin, but only in those subjects previously demonstrating adequate saturation.[1418]

Observations concerning the fate of carbon 14-labeled hydrocortisone revealed that over 90% was excreted as urinary conjugates within 72 hours,[943, 1621, 1622] and that excretion curves were the same whether the steroid was administered orally or intravenously, indicating complete absorption from the gastrointestinal tract.[1621] Hydrocortisone was found to disappear rapidly from the vascular compartment.[1825] Carbon 14-labeled preparations were promptly absorbed by the liver, excreted in the bile, reabsorbed from the gut, recirculated, and finally excreted in the urine.[1621, 1639, 2260] In a patient with biliary fistula, absence of steroid in the feces indicated that there was no excretion through the intestinal mucosa.[1621]

Conjugated urinary steroids appeared to be predominantly glucuronides.[1621] In the rat, more rapid disappearance of hydrocortisone from the circulation than could be accounted for by simple diffusion suggested that degradation is preceded by fixation to tissue.[1246]

Four urinary metabolites of hydrocortisone were described which were nonreducing steroids and thus might be overlooked by assay methods depending on reduction reactions.[733] The urinary metabolites of corticosterone were found to differ from those of progesterone, desoxycorticosterone, cortisone and hydrocortisone.[633]

The potencies and metabolic properties of cortisone and hydrocortisone could be altered by the introduction of a double bond at carbon-1 or halogen substitution (see above—New Synthetic Steroids). From studies of the metabolic properties of 11-, 17-, and 21-hydroxy derivatives of progesterone and their 9 alphafluorinated derivatives, the following conclusions were supported: (1) the 11 beta-hydroxyl group appeared to be essential for glucocorticoid activity, but in the presence of a 21 alpha-hydroxyl group there was decreased sodium-retaining activity; (2) the 17 alpha-hydroxyl group increased the glucocorticoid activity; (3) the 21 hydroxyl group enhanced the sodium-retaining activity.[805] The effects of either cortisone or corticotropin on nitrogen excretion were not influenced by large doses of potassium chloride.[1797] Large doses of hydrocortisone given intravenously caused an early rise in serum potassium, suggesting a shift of intracellular fluid to the extracellular compartment.[1156]

Flexion deformities in the extremities of three female patients with Addison's disease were attributed to adrenal and pituitary insufficiency, "probably because of hydrocortisone deficiency."[2135] [No evidence given.—Ed.]

Mode of Action. The mechanism by which adrenal steroids or corticotropin suppresses arthritis and other inflammatory diseases remained obscure. It was proposed that cortisone and related compounds partially protect the tissues from damage resulting from a union of allergens and fixed antibody, i.e., their activity is "anti-allergic."[1294] [In spite of the vast number of fundamental studies in different species, and extensive clinical observations, the exact mechanism of the anti-inflammatory effect of the corticosteroids is still shrouded in mystery. The true importance of the discovery of cortisone is that it has provided a major research tool, and its use as such in the connective tissue diseases has scarcely begun.—Ed.]

Investigations of the metabolism of steroids injected into the joint suggested that anti-inflammatory effects might be due to a specific metabolite of hydrocortisone.[2233] Hydrocortisone gave rise to at least three other corticosteroids—11 β-hydroxy-Δ4-androstene-3, 17-dione and several other 17-ketosteroids. Fischer described the histologic changes induced by adrenal steroids, and included degranulation and vacuolation of the mast cells and disappearance of metachromasia without alteration of round-cell infiltrates.[688] [This comprehensive survey covered 754 references to important contributions relating to corticotropin and cortisone in rheumatoid arthritis up to the autumn of 1954.—Ed.] An investigation of the fate of radioactive, colloidal chromium phosphate in rats showed that cortisone depressed the ability of reticuloendothelial cells to phagocytize and regenerate.[941]

When steroids were injected locally into non-inflamed tissue, hematoxylin-staining masses appeared without a significant inflammatory reaction. Pyknosis and karyorrhexis of adjacent connective tissue cells were observed. Mechanisms for local suppression of inflammation were not explained.[807, 808] The cortisone effect on rheumatoid disease was found to be blocked by vitamin B_{12}.[1290] The potency of cortisone was not influenced by concomitant administration of desoxycorticosterone.[825] A possible relationship of steroid-induced remissions to the ameliorating effects of pregnancy seemed questionable in view of a report of patients whose arthritis was aggravated by pregnancy but relieved by cortisone.[824] [The intriguing, if not explained, relationship between the physiologic effects of pregnancy in rheumatoid patients and the effects of adrenocortical steroids still merits further study.—Ed.]

Total adrenalectomy in a 38 year old female with severe rheumatoid arthritis only partially controlled by 50 to 100 mg. of cortisone a day resulted in striking subjective and objective improvement.[1457]

Therapeutic Results. Except for dosage factors, the clinical effects of corticotropin, cortisone, hydrocortisone, prednisone, prednisolone and fludrocortisone were similar.[294, 429, 638, 830, 913, 1776, 1793, 2143, 2205, 2244] Early disease was found to be more responsive.[290, 638] Subjective improvement in the patient was more striking than was objective improvement,[279, 638] and x-ray evidence of disease progression during therapy was frequently noted.[213, 215, 218, 289, 290, 429, 632, 638, 975, 2205] Such progression was observed in 33% of patients treated[213, 215] and did not correlate with the clinical state.[218] Remissions of the rheumatoid process were observed during hormone therapy in a "mere 8% of cases."[213, 215] Although in one study only 6% of patients failed to derive some benefit from steroids,[290] in another, failures were reported in 95% at the end of four years of treatment.[975]

Of 150 consecutive patients treated with hydrocortisone, "adequate" improvement was observed in 59% and "unsatisfactory" in 41%. Dosage levels averaged 40 to 65 mg. per day for severe cases and 25 to 40 mg. per day for moderate cases. Treatment was discontinued in 16% for the following reasons: insufficient response (2.7%); major complications (1.3%); unrelated complications (0.7%); death from other causes (3.3%); natural remissions (8%).[213, 215]

In four separate series of cases, criteria recommended by the Therapeutic Trials Committee of the American Rheumatism Association were applied, with the following results: Grade I response was observed in 18%[638] and 23%[290] of patients treated with cortisone, and 0%[1349] and 41%[830] of patients treated with prednisone. Grade II response occurred in 27%[638] and 28%[290] in the two cortisone series, and in 50%[1349] and 46%[830] in the two prednisone series. Grade III response occurred in 7%[638] and 42%;[290] and 50%[1349] and 11%.[830] Grade IV response was observed in 48%,[638] 7%,[290] 0%[1349] and 2%.[830]

Functional improvement was most impressive, with 25 of 31 patients becoming self-sufficient,[290] and 18 of 24 patients becoming employable.[1001] Hormone therapy was found to be a valuable adjunct to physical medicine[122, 126, 289, 290, 638] and vocational rehabilitation.[1033, 1115]

Hypercortisonism induced by continuous administration of corticotropin or corticosteroids was considered to be a prerequisite for effective long-term hormone therapy.[2244] Relapses were observed in 80% of patients receiving steroid therapy following cessation of treatment.[292]

A compilation of experiences with prednisone in 721 rheumatoid patients showed excellent or good results in 97%, and fair or poor results in 3%.[945] [Therapeutic criteria, dose and duration of therapy were not indicated.—Ed.]

A coöperative study of the effectiveness of cortisone in the management of rheumatoid arthritis was conducted by a committee of the American Rheumatism Association. Data derived from information on 546 patients revealed the ratio of favorable to unfavorable response at the end of two years to be 3:7 in terms of grade of response, and 4:6 in terms of functional improvement.[32] [Dosage schedules were variable but generally were higher than are now considered to be desirable for long-term administration.—Ed.]

The relative efficacy of cortisone and aspirin in the treatment of early cases of rheumatoid arthritis was investigated by a committee representing the British Medical Research Council and the Nuffield Foundation. One hundred patients were selected, ranging in age between 17 and 60, and having rheumatoid arthritis in three or more joints. Treatment consisted of a basic regimen of general care plus either cortisone or aspirin. Cortisone dosages began at 75 mg. per day and were adjusted to the lowest dose which controlled symptoms. The aspirin dosage was initially 4 gm. per day, and adjusted as necessary. Results of therapy were tabulated at the end of six months and one year. No significant differences were observed between the two groups in regard to progression of the disease, functional capacity and laboratory findings.[590, 632, 1420] This report was quickly challenged as being highly inaccurate in its method of grading improvement. In evaluating results it completely ignored such important clinical features as the degree of stiffness and the patient's sense of well-being.[588] [This study has not only demonstrated the effectiveness of aspirin but has also emphasized the need for methods by which more meaningful therapeutic trials can be

conducted. It did not consider the effectiveness of steroids combined with aspirin, commonly administered in practice.—Ed.]

Effects on Laboratory and Pathologic Manifestations. Abnormal serum protein patterns reverted toward normal under the influence of adrenal hormones. Fibrinogen and globulins decreased, while albumin increased.[41, 683]

Serial studies of synovial fluid showed an increase in viscosity and decrease in polymorphonuclear leukocytes during treatment.[1755] Positive evipan tests observed in rheumatoid patients with elevated flicker-fusion values became negative during the administration of corticotropin.[1537] Cortisone was found to correct abnormal thermal responses to blood flow in rheumatoid patients.[2252]

Rheumatoid nodules were observed to be softer and smaller during treatment, but without a significant change in histologic characteristics. Bilaterally symmetric subcutaneous nodules were studied in eight patients with rheumatoid arthritis of from two to 29 years' duration. In all patients, softening and a decrease in volume occurred during the administration of cortisone. On microscopic examination, greater than usual degrees of inflammation, necrosis and palisading were observed in five nodules removed during treatment. In other instances there was lessening or disappearance of inflammatory activity with striking degrees of fibrosis.[2295] Serial biopsy studies of dermal connective tissue from rheumatoid patients during hormone therapy showed disappearance of metachromasia, degranulation and vacuolation of mast cells. Round cell infiltrates were unchanged.[682]

Hematologic findings in four patients with rheumatoid arthritis treated with prednisone were reported.[2096]

Comparative Effects of Steroids. When comparative effects were observed, 50 mg. of hydrocortisone were estimated to be equivalent to between 80 and 85 mg. of cortisone acetate.[2201] Prednisone was estimated to be two to five times more potent than cortisone and hydrocortisone on a milligram-for-milligram basis.[294, 899, 913, 2169] Prednisolone was found to have the same potency as prednisone.[294]

The ideal maintenance dose of steroids was concluded to be one that controls the disease most of the time without side-effects.[1001, 1972, 2170] It was recommended that the maintenance dose should relate to individual tolerance rather than to degree of suppression.[683] Although increasing dosage for exacerbations was thought unwise,[1972] an increase for a predetermined period was considered to be appropriate.[2170] Initial high doses with dramatic effects were found to be less desirable than were smaller initial doses with a slower rate of improvement.[432, 433, 1823] In disagreement with this view were studies of the effects of large initial suppressive doses, from which it was concluded that long-range side-effects were no greater, and the "salvage rate" was higher.[1144] Moreover, larger initial doses were advised in recommendations for the use of prednisone.[945] [The ultimate value of initial large doses of hormones has never been clearly established. The majority of the co-authors favor starting with low doses and slowly increasing.—Ed.]

For severe cases, the average maintenance dose of hydrocortisone was calculated at 40 to 65 mg. per day, and for moderate cases at 25 to 50 mg. per day.[213] The optimal maintenance dose of cortisone was found to be approximately 50 mg. per day.[1823] [Needs also dependent upon the age and sex of the patient.—Ed.] The effective maintenance dose of prednisone was estimated to be 5 to 20 mg. per day.[945] For intra-

articular administration of hydrocortisone, average doses of 25 mg., ranging from 5 to 37.5 mg., depending upon the size of the joint, were found to be adequate. For intravenous administration of hydrocortisone, doses of 100 to 500 mg. per day were administered.[1793, 1794] [The use of intravenous hydrocortisone in rheumatoid arthritis is restricted to situations where the steroid-treated patient has been or is about to be exposed to acute stress, such as surgery, in which a state of relative adrenal insufficiency may exist. —Ed.]

Corticotropin. Corticotropin gels were found to vary in potency.[821, 2204] Reliable methods for assessing adrenal cortical function were considered to be essential to the intelligent use of corticotropin.[2203, 2204] Daily injections of corticotropin effecting an increase of 40 mg. of 17-ketogenic steroids were found to be equivalent to 100 mg. of cortisone.[2203] It was observed, also, that 17-ketosteroids did not always correlate with 17-ketogenic steroids.[2204] [17-ketogenic steroids are corticosteroids that can be oxidized to 17-ketosteroids, and hence are an index of the elaboration of certain corticosteroids by the adrenal cortex.—Ed.]

Method of Administration. Oral Steroids. Clearances of 17-hydroxysteroids from plasma following the ingestion of cortisone and hydrocortisone were variable, and related primarily to the physical form of the preparation ingested. Microsuspensions were quickly absorbed, with a peak blood level occurring in one hour, and cleared more rapidly. Following oral ingestion of tablets, peak levels were lower and the plasma clearance was slower than were those observed with suspensions. Oral tablets permitted more accurate control of the height and duration of plasma levels.[612] Hydrocortisone was found to be more potent than cortisone by the oral route.[1193] Division of doses into at least four parts per day was advised.[213, 2170]

Intravenous Steroids. Hydrocortisone was found to be more potent than cortisone when given intravenously, and both were more potent by this route than when given by mouth.[1193] [A large fraction of administered cortisone (given intravenously, intramuscularly or orally) has been found by Peterson et al. (J. Clin. Investigation **36**: 1301 (Sept.) 1957) to be rapidly converted to hydrocortisone. It may be that most of the biologic activity of cortisone resides in that fraction that is converted to hydrocortisone.—Ed.] The intravenous administration of hydrocortisone resulted in a rapid hormonal effect.[910, 1509, 2170] Urinary steroids were suppressed by a single dose of 100 mg. of hydrocortisone given in this manner over an eight-hour period.[1794] It was advised that intravenous injection of steroid should always be supplemented by orally administered steroid.[1793, 1794] [But this often is not possible in the acutely ill patient.—Ed.]

Corticotropin. Effective long-term corticotropin therapy was achieved by the administration of preparations delaying absorption of the hormone.[1569, 1962, 1963, 2203] Zinc precipitates of corticotropin were found to be resistant to destruction by serum enzymes.[1570] A single injection of 20 units of corticotropin-Z (zinc) resulted in an eosinopenia lasting 24 hours, and two injections per week provided continuous suppression of rheumatoid arthritis.[1569] Allergic reactions and diminishing responsiveness to depot-therapy were observed.[1962, 1963, 2203] Only small doses of corticotropin were necessary to suppress rheumatoid activity when infused intravenously.[126, 401]

Intra-Articular Steroids. The injection of hydrocortisone and certain of its esters into inflamed joints was reported to be useful in the amelioration of local manifestations [228, 301, 308, 398, 563, 978, 981, 1115, 1724, 1802, 1824, 2155, 2195, 2272] as an aid to rehabilitation [563, 1755, 2195] and when but one or two joints were involved.[301,

[1972, 2195] Various technics of injection were described.[82, 949, 1332] The effects of the intra-articular administration of 12 esters or analogues of hydrocortisone were studied; tertiary butyl acetate was found to be most effective in this group.[981] The potency and long-lasting effect of hydrocortisone tertiary-butyl acetate were confirmed by others.[173, 563, 721, 977] Although fludrocortisone acetate was observed to have anti-inflammatory activity when injected intra-articularly, its use was not advised, since sufficient absorption occurred systemically to result in marked edema.[979] Hydrocortisone acetate was considered to be more active intra-articularly than was hydrocortisone free-alcohol in a comparison of the merits of these two preparations.[72]

Abnormal synovial fluid patterns reverted toward normal after intra-articular injections of hydrocortisone. Increases in viscosity and decreases in both the total cell count and percentage of polymorphonuclear leukocytes were observed.[72, 563, 1755] Viscosity was found to increase in the absence of other anti-inflammatory effects.[72] Increases in viscosity were not associated with changes in polysaccharide or protein concentrations. However, there was a decrease in water-binding capacity and an increase in the amount of reactive amino groups and protein glucosamine.[1184]

Hydrocortisone disappeared more rapidly from the joint than could be explained by simple diffusion.[475] Chromatographic separation studies of metabolites of steroids injected into joints suggested that inflammation is suppressed by a metabolite of hydrocortisone. Hydrocortisone was metabolized into three distinct corticosteroids, and cortisone into hydrocortisone plus several other steroids. When eluates of chromatographed synovial fluid from joints treated with hydrocortisone were instilled into granuloma pouches, anti-inflammatory effects were observed only when fluid had been aspirated three hours after injecting the steroid.[1405, 2222] It was observed that hydrocortisone acetate was taken up and stored by the synovial cells.[2280] The rates of disappearance of cortisone, hydrocortisone free-alcohol, and hydrocortisone acetate were approximately the same.[2280, 2281]

The effectiveness of intra-articular steroid therapy in controlling local symptoms was demonstrated in several studies. In a series of 60 patients, 1,020 injections were made into 105 joints. There was sustained benefit in 50%, moderate improvement in 31%, and no favorable effects in 19%.[563, 1755] In another group of 35 patients, 40% had subjective and objective benefit, 43% subjective benefit, and 17% no benefit from this method of therapy.[228] In still another series of 144 patients who received 940 injections, 72% were markedly improved, 24% moderately improved, and 3% unimproved.[1972] Injections were required at from one- to 2.8-week intervals.[228, 1972] In the majority of instances, benefits were usually temporary;[2195] however, 19% of 105 treated joints remained improved after repeated injections were discontinued.[563, 1755] Complications occurred in 2.4% of 10,000 intra-articular injections, including two cases of infectious arthritis.[978] Local infection was reiterated to be a contraindication for local steroid therapy.[1972] That intra-articular injections of hydrocortisone are not without danger was evident in a report of six infected joints which followed this procedure.[1087] [When one considers the number of treatments given, the incidence of this complication is rare. However, ordinary aseptic technic should be followed with care and prompt treatment instituted if a septic arthritis occurs. Intra-articular steroid therapy is seldom indicated in long-term management of rheumatoid disease.—Ed.]

Complications of Hormone Therapy. The incidence and severity of major complications correlated with dosage and duration of treatment.[212, 213, 2177] Serious complications were estimated to occur in from 5 to 10% of patients treated.[292] In a series of 59 cases, one or more undesirable side-effects appeared in 84%

of females and 70% of males.[289, 290] A coöperative study of the effects of cortisone in 546 patients revealed that 46% developed major complications and 72%, minor complications. The most frequent untoward effects were the classic somatic manifestations of induced or endogenous hyperadrenalism, including obesity, moon-face, hirsutism and acne.[289, 290, 433, 638, 683, 768, 888, 1001, 1115] Such somatic changes also occurred during the administration of prednisone.[294, 399, 541, 830, 1349, 1456, 1508, 2143] Edema resulted from therapy with hydrocortisone, cortisone or corticotropin,[279, 638, 683, 768, 888, 1001] and fludrocortisone,[211, 214, 804, 882, 2143, 2168, 2169] but much less frequently with prednisone or prednisolone.[219, 294, 399, 541, 830, 1349, 1456, 2143] Cardiovascular complications were occasionally associated with the use of all active hormones, and included hypertension,[279, 290, 433, 638, 683, 888, 1115, 2177] cardiac arrhythmias,[279, 683, 888, 1349] cardiac enlargement,[683, 888] electrocardiographic abnormalities,[683, 768, 888, 2101] congestive failure,[647] angina pectoris or precordial distress,[768, 830] and cerebrovascular accidents.[433, 830] Those cardiovascular abnormalities precipitated by edema were not apparent in patients treated with prednisone.[945]

Aggravation of diabetes, impaired glucose tolerance, hyperglycemia or glycosuria were induced occasionally by corticotropin, hydrocortisone, cortisone and prednisone.[219, 279, 290, 399, 433, 498, 541, 683, 768, 830, 888, 1508, 1645] Instances of osteoporosis and spontaneous fractures were noted.[289, 290, 472, 615, 638, 683, 888, 2101]

Psychic and central nervous system disturbances included headache, insomnia, euphoria, depressions and hallucinations.[289, 290, 433, 638, 683, 691, 768, 888, 1001, 1302, 2101] Such complications occurred during prednisone therapy, and resembled those previously recognized with cortisone or hydrocortisone.[219, 294, 399, 541, 830, 1349, 1456, 2143] The problem of induced psychoses was considered. It was concluded that no satisfactory explanation had evolved, and that it was not possible to predict which patients would develop mental aberrations.[691, 1672, 1794] The onset of psychotic reactions seemed to relate to three variables, namely, pharmacologic effects of the hormone, the meaning to the patient of alteration of symptoms, and fantasies concerning the action of the substance given.[705] Two types of psychoses were described: (1) an affective psychosis which continues after withdrawal, [1105, 1302] and (2) an organic type which stops when hormone is discontinued.[1105] Behavioral changes could not be induced experimentally in normal[357] or psychotic subjects.[1252] Intravenous injections of hydrocortisone were found to induce seizures in susceptible patients,[1794] and may increase theta wave activity in the electroencephalogram. The induced changes in the electroencephalogram could not be correlated with abnormal mental states.[790]

Gastrointestinal Complications. Mild to serious complications of the gastrointestinal tract were attributed to hormone therapy, and ranged from epigastric distress to hemorrhage and fatal perforation.[219, 294, 399, 541, 683, 768, 830, 888, 1349, 1579, 2101, 2143] Adrenal hormones were believed to predispose to peptic ulceration.[593] This complication was observed during treatment with corticotropin, cortisone,[76, 101, 150, 289, 290, 433, 554, 615, 638, 676, 683, 888, 1115, 1455, 1911, 2101, 2247] and prednisone.[219, 945, 1349] A survey of the literature revealed the incidence of peptic ulcer during cortisone therapy to be 5.3%, whereas a compilation of reports on complications of prednisone therapy showed an incidence of only 0.6%.[945] [Subsequent studies have raised this incidence.—Ed.] Nevertheless, in one series of 18 patients carefully observed during prednisone therapy, three developed peptic ulcers.[219] There was little correlation between dose of the hormone and their occurrence.[2247] [We cannot agree.—Ed.] Moreover, remissions of ulcer symptoms during hormone therapy were cited, and the incidence of ulcers developing while on steroid therapy correlated poorly with previous episodes.[1816]

Experimental studies of gastric function in normal human subjects showed that corticotropin increased the mean concentration of pepsin and hydrochloric acid, decreased viscosity and mucin content of gastric secretion, and increased urine pepsinogen.[971] Similar increases of urine pepsinogen were observed during the administration of cortisone, hydrocortisone and corticosterone.[831]

The occurrence of a gastric ulcer in a patient with Addison's disease during treatment with cortisone suggested that adrenal hormone is necessary for but is not the cause of the ulcer, and that, in the presence of an excess of adrenal hormone, the stomach and/or duodenum may be sensitized to respond with secretory hyperactivity and/or ulceration to stimuli which would ordinarily be innocuous.[2052]

In experimental gastric ulceration where Mann-Williamson dogs were used, fewer complications occurred during hormone therapy than in controls.[1817] When corticotropin was administered to dogs, it resulted in increased volume, acidity, pepsin, chloride content and osmolarity of the gastric secretion. This response could be altered by adrenalectomy but not by vagotomy.[2144] In rabbits, cortisone diminished inflammation and inhibited fibroplasia but not epithelization of induced ulcers.[2225] [Peptic ulceration is occasionally a troublesome accompaniment of hormone therapy. The precise relationship of its occurrence to the dose, duration of therapy and nature of the agent used is not known, due to limitations of methods for studying the incidence of peptic ulcer. However, recent studies have shown that the risk of developing a peptic ulcer during treatment with adrenocortical hormones is increased by at least 25%. Such ulcers also occur more often in patients receiving more than 50 mg. per day of cortisone, or 20 mg. per day or more of prednisone or prednisolone.—Ed.]

Infection. Serious infections complicating hormone therapy were observed, including tuberculosis,[647, 682, 1261, 1544] fulminating pneumonia,[1026, 1575] moniliasis and aspergillosis,[1249] and a variety of systemic and localized infectious processes.[279, 550, 683, 888, 1911, 1961] Suppression of symptoms of fatal infections was described.[1574] The influence of ACTH and cortisone on the incidence of infections in 44 patients with rheumatoid arthritis was observed during 465 months of hormone therapy and for 411 months without such medication. There were nine and 16 infections, respectively. It was concluded that therapeutic doses of ACTH and cortisone did not exert a pronounced effect on the incidence of infections in these patients.

Observations and hypotheses concerning the effects of adrenal hormone therapy or resistance to infection included the following: (1) lowering of host resistance, (2) impedance of antibody formation, (3) interference with local antibody reactions, (4) prevention of reflex vasoconstriction, (5) delay of movement of colloidal and particulate materials through the ground substance, and (6) altered permeability of blood vessels.[2084] It is of interest that corticosterone, although similar to hydrocortisone in metabolic effects, did not influence resistance to experimental infections.[1088, 1089] An entirely new approach to steroid therapy in the management of severe infections has been popularized by Kinsell.[1143] He advocates the use of combined corticoid-antibiotic therapy in seriously or critically ill patients over a period of from four to seven days. The principle on which this procedure was based was to combat shock and toxemia from overwhelming infections where it is doubtful whether the patient would survive sufficiently long to permit the action of antibiotics.[708]

Induced Adrenal Cortical Insufficiency. Suppression of adrenal cortical function was observed during the administration of hydrocortisone, cortisone, fludrocortisone, prednisone and prednisolone.[291, 294, 498, 715, 747, 804, 882, 1508, 1721, 1794, 2143, 2202] Adrenal cortical insufficiency was also observed after cessation of corticotropin therapy.[279, 683, 1823, 1858] [The adrenal insufficiency is probably secondary, and reflects long-term inhibition of the anterior pituitary.—Ed.] Circulatory collapse after surgery or similar stress occurred in several hormone-treated

patients,[1528, 1592, 1793, 1794] and in some instances terminated fatally.[554, 1911] Atrophy of the adrenal cortex was said to have been prevented by the weekly injection of 150 to 200 mg. of corticotropin.[2245] [The effect of such therapy on the pituitary was not elucidated. The routine use of ACTH is not recommended with long-term steroid therapy.—Ed.]

Adrenal glands from 190 patients treated with cortisone for a variety of diseases revealed uniform changes, irrespective of the conditions treated. Although it was reaffirmed that cortisone was capable of inducing adrenocortical atrophy, the factors of dosage, duration of administration and time necessary for recovery could not be determined. It was established, however, that atrophy and depression of function may persist for weeks or months after withdrawal of the steroid.

The pituitary glands of 77 patients treated with cortisone or corticotropin showed degenerative changes of the basophils consisting of degranulation and hyalinization. There was strong evidence that cortisone-induced adrenal atrophy was secondary to suppression of endogenous corticotropin.[147]

[It now seems clear that both carbohydrate-active steroids and corticotropin suppress pituitary function and impair the individual's ability to respond to stress. Although adrenal cortical atrophy may be prevented by the concomitant administration of corticotropin, the suppression of endogenous secretion of corticotropin is not. There is no proved physiologic basis for the administration of corticotropin during or after steroid therapy for the purpose of preventing or correcting adrenal cortical insufficiency.—Ed.]

The hazard of surgery in patients receiving adrenal hormones was emphasized.[2, 1604] It was advised that all patients receiving steroids should be prepared prior to surgery by the administration of cortisone 24 hours or more preoperatively or be given repeated intravenous injections of hydrocortisone.[749, 1604, 1858, 1911, 2170, 2292] Specific and detailed suggestions for the management of patients with hypocorticalism who require surgery were described.[1528] [Adrenocortical insufficiency is a serious threat in patients who have been receiving therapy with cortisone or other corticosteroids and who undergo emergency or elective surgical intervention. Special preparation for operation is recommended for any patient who has received these drugs within three to six months. Stress-imposing reactions before, during and after anesthesia should be avoided. An increased amount of corticosteroid preoperatively for two or three days using cortisone intramuscularly in doses of 100 to 200 mg. daily is recommended. Postoperatively, cortisone is given in diminishing doses for from two to three days. One must be prepared to treat arterial hypotension with 100 mg. of hydrocortisone in a liter or less of saline, repeating this quantity in from one to four hours if needed. In acute emergencies when this schedule cannot be followed, it is recommended that intramuscular cortisone be given and intravenous hydrocortisone be added and continued during the postoperative period and the immediate convalescent period, if necessary.—Ed.]

Thrombophlebitis and thrombo-embolic phenomena were observed,[13, 638, 683, 888, 1001, 1701, 1961, 2101] and on occasions were complicated by pulmonary infarction.[13, 647, 1961] In four cases, thrombo-embolic phenomena were associated with hypercholesterolemia,[13] ecchymoses [683, 888] and purpura.[290] Cases of diffuse vasculitis similar to periarteritis nodosa were observed [279, 638, 676] which in one instance resulted in gangrene.[638] [There is a growing belief that steroid therapy of rheumatoid arthritis may be responsible for the occurrence of or accentuation of widespread vasculitis accounting for clinical manifestations similar to those of periarteritis nodosa. It is noted that rheumatoid vasculitis

occurs rarely in untreated patients. It is being seen more frequently in those receiving adrenal steroids or corticotropin. See "Vasculitis" under section on Pathology of Rheumatoid Arthritis.—Ed.]

The pathogenesis of thrombo-embolic phenomena was not clear. In 30 patients studied, neither cortisone nor corticotropin altered prothrombin-proconvertin concentrations; however, a slight decrease in clotting time and platelet count was observed in six cases.[682] Anticoagulants administered simultaneously with cortisone decreased the incidence and in some instances prevented recurrences of thrombophlebitis.[1701]

Other abnormalities attributed to hormone therapy were menstrual irregularities,[290, 683, 888, 1001] delayed wound healing,[433, 683, 768, 888, 1115, 1961] increased sweating attributed to prednisone,[294, 541, 830, 2143] paresthesias,[290, 683, 888] weakness,[290, 294, 541, 638, 830] renal disease (albuminuria and uremia),[279, 1001] urinary frequency[541] and hypokalemia.[683, 888]

Fatalities occurred during hormone therapy which in some cases could be directly attributed to the effects of the agents used, but in others had a questionable or remote relationship.[279, 433, 554, 638, 676, 1088, 1249, 2101]

Potentiation of Hormone Effects. The combined administration of para-aminobenzoic acid and cortisone in 30 patients appeared to result in degrees of improvement usually observed with much larger doses of cortisone.[2215] [This has not been generally confirmed.—Ed.]

Chrysotherapy. It was pointed out that the majority, but not all, of the clinicians experienced in therapy of rheumatoid arthritis believed that there was considerable merit in gold therapy.[292] Support for the potential effectiveness of gold came from many sources.[617, 1276, 1681, 1693, 1787, 1845, 2111] The mode of action of gold has not become known.[292] It was observed that, of 20 patients developing hypersensitivity reactions to gold, 14 experienced "100 percent remissions" of disease, suggesting that patients responding best to gold have some degree of hypersensitivity.[1681]

The fate of gold was studied by the administration of radioactive colloidal gold (Au^{198}) intravenously in man. Radioactivity was observed to disappear rapidly from the bloodstream, and was deposited largely in the reticuloendothelial system.[1769]

Both gold thioglucose and aurothioglycanide in oil suspensions were found to be effective.[1693, 1845, 2111] The value of colloidal gold suspensions was questioned.[1681]

Selection of cases for gold therapy was considered to be an important factor determining results, with emphasis on the presence of confirmed rheumatoid activity and early disease.[1693] Doses of 25 mg. per week for two weeks, then 50 mg. per week until a total of 1,400 to 1,500 mg. has been given, were found to be satisfactory.[1681]

Few data were available concerning results of gold therapy. Of 36 patients treated over a 15 year period, 84% had experienced subjective improvement by the end of the second month and 47% were "completely rehabilitated."[1693] Of 56 patients, 41% had a major response to therapy; the lower percentage of improvement was attributed to the more advanced disease.[1845]

Toxic reactions were estimated to be severe enough to necessitate interruption of therapy in 10 to 20% of cases.[292] Of 56 cases (vide supra), eight developed skin rashes and one, thrombocytopenic purpura.[1845] In a study of toxic manifestations of gold therapy in 173 patients, it was noted that leukopenia and albuminuria occurred more frequently in patients with low sedimentation rates, whereas dermatitis and

eosinophilic reactions did not, suggesting that the former are toxic phenomena due to saturation with gold and the latter are allergic responses.[1078] Three additional cases of serious bone marrow suppression, one fatal, were described.[1664, 2088] In one, neurologic manifestations suggesting hemorrhages into the spinal cord and brain stem appeared.[2088] A high incidence of liver damage was found in patients developing skin reactions.[1198] Decreased fatalities were attributed to the effectiveness of dimercaprol (BAL) and adrenal hormones in combating toxic manifestations.[292] One case of gold toxicity uncontrolled by dimercaprol because of inadequate dosage, and another that responded to dimercaprol but not to ACTH, were described.[2088]

The effects of combined gold and adrenal hormone therapy were studied in 50 patients with severe rheumatoid arthritis. Results were similar to those with gold alone.[172]

[The value of gold therapy continues to have solid support from those clinicians most experienced in its use, but statistical proof of its efficacy is still lacking.—Ed.]

Miscellaneous Agents. Nitrogen mustard was reported to have a favorable effect on the clinical and laboratory manifestations of rheumatoid arthritis.[1590, 1722] Of 17 patients with severe active disease given 0.1 mg. of nitrogen mustard per kilogram body weight for four consecutive days, eight experienced major improvement and nine, minor improvement. Calcium balance became positive and abnormalities of serum proteins were altered toward normal. The duration of benefit was from six to 32 weeks.[1590] In another series of 12 patients, all were improved, although in most cases benefit was slight and of short duration.[1722] [These studies were carefully performed but both series were small. There is a need for further investigation.—Ed.]

A solution of formic acid, silicic acid and cobra venom was reported to be of value in "all types of arthritis," including rheumatoid arthritis.[282, 1317] [These reports are meaningless; results were not classified by disease, and specific objective criteria for improvement were not applied.—Ed.]

Hexamethonium chloride was administered to 12 patients for periods of from two to nine months and resulted in subjective and, in some instances, objective improvement in 11.[1641] [Critical criteria for improvement were not applied.—Ed.] Because of a reportedly high incidence of amebiasis in patients with rheumatoid arthritis, 25 patients were treated with Diodoquin and/or chloroquine. "Major improvement" was observed in 16 patients.[1736] [A flurry of interest has followed this and other favorable reports by Bagnall [83] and Cohen and Calkins.[402] Other experienced observers are not impressed with the results of therapy with this drug. There is a growing appreciation of the need for more reliable methods for evaluating new agents introduced for the treatment of rheumatoid arthritis. Until satisfactory technics are evolved, chloroquine and other drugs will have to be judged by the slow and expensive but only currently accepted method, "the test of time."—Ed.]

Six patients given injections of trypsin in oil, intramuscularly, derived no subjective or objective benefit.[813] Adenosine triphosphate, given to 25 patients, improved vasomotor symptoms but did not alter the rheumatoid process.[931] Embryonic bone marrow, defatted, deproteinized and supplemented with malic acid (Cerbartrol) resulted in "improvement" in one of 17 patients.[1942] [Criteria not stated.—Ed.] *Phytolacca american* (Indian pokeroot) was administered to 21 patients with unclassified arthritis, with improvement in pain in 53%.[1185] Two organic copper compounds (alcuprin and cuprimyl) were found to be of no value in 10 well established cases of rheumatoid arthritis.[1563]

Desensitizing doses of aqueous extracts of streptococci, administered to 51 patients for periods of more than two years, were found to be of benefit.[1931] [No data concerning therapeutic results.—Ed.] Subcutaneous injections of hyaluronidase in the

vicinity of involved joints relieved pain but was less impressive in rheumatoid arthritis than in other types of joint disease.[1758] Sodium tri-ketocholonic acid injected intramuscularly benefited 64% of 56 patients.[961] One patient treated successfully with typhoid vaccine was reported.[1964] Irradiation of sympathetic ganglia was reported to be beneficial to peripheral joints.[681]

Infiltration of painful areas with local anesthetics was recommended in the treatment of nonarticular and articular rheumatism, including rheumatoid arthritis, with less satisfactory results in the latter.[933, 1276] Intradermal injections of minute amounts of procaine resulted in improvement in 60% of 133 patients with rheumatoid arthritis.[425]

Relaxants were subjected to clinical trials, with subjective and sometimes objective benefit. A combination of mephenesin, salicylamide and ascorbic acid relieved pain and spasm in a variety of rheumatic diseases, including rheumatoid arthritis.[1513] Reserpine temporarily relieved musculoskeletal complaints in one of four patients with rheumatoid arthritis.[108] A new cholinergic compound (Stigmonine Bromide) had a favorable effect on pain and limitation of motion.[1497]

The effects of transfusions of prepartum and postpartum plasma and injections of placental extracts on rheumatoid arthritis were evaluated, as were implantations of placental tissue.[516, 1071, 1274, 1275, 1523] Transfusions of blood from pregnant women resulted in partial and unpredictable amelioration of symptoms in some patients, but this was not comparable to the remissions of pregnancy.[1071] Infusions of postpartum plasma had no significant effect on the disease in 11 patients.[1523] Placental extract was administered to 18 patients, with improvement reported in all.[516] Direct implantation of placental tissue was reported also to have beneficial effects.[1275]

Relaxin, a hormone of pregnancy,[2286] was administered to two patients without effects on the disease.[1608]

[A variety of new treatments for rheumatoid arthritis continue to be tried which seldom fail to benefit the patient. Thus, this and previous Rheumatism Reviews have included a great many references to early observations often published prematurely and without adequate control studies. These one-paper authors either never pursue their investigations or discover after additional trials that the therapeutic benefit was apparent rather than real, and never record the less favorable follow-up data. The need for more long-term controlled clinical studies of new therapeutic agents is obvious.—Ed.]

Psychotherapy. The role of psychotherapy in the management of patients with rheumatoid arthritis has not yet been clarified.[1681] It was stated that some regression to dependent or infantile attitudes proportional to the degree of helplessness incurred is an accompaniment of every illness or injury. Normally this regression subsides with convalescence. In persons with unresolved dependency conflicts, the reactivation of the conflict by the occurrence of disease or injury which forces the subject into a dependent position may interfere seriously with treatment. In severe chronic cases of rheumatoid arthritis, dependency conflicts may become important, and the interference with reality in itself constitutes a stress which may precipitate neurotic symptoms. Furthermore, the patient may enlist his organic disorder to solve other conflicts.[1816]

Deep psychotherapy was not considered to be very effective.[1681] Observations on eight patients treated for from six months to several years indicated no definite effects of analytically oriented psychotherapy on the disease, although two patients were markedly improved.[1816] Nevertheless, it was believed that emotional factors have an important relationship to rheumatoid arthritis.[94, 276, 1816] The use of d-amphetamine sulfate resulted in a feeling of well-being and alleviation of pain in 34 of 54 patients, suggesting a relationship of physical symptoms

and mood.[94] [Further study in this important aspect of the disease is surely indicated.—Ed.]

Physical Therapy. The importance of and details referable to physical therapy in the treatment of rheumatoid arthritis were again emphasized.[110, 128, 640, 1173, 1659, 1891] The value of simple procedures useful in the home was stressed.[1472] An inexpensive homemade whirlpool bath was described.[191] Though neither cortisone nor corticotropin had displaced physical therapy, their use permitted more effective joint function.[128]

The increasing importance of *remedial* or *therapeutic exercise* was being increasingly recognized.[963, 1595, 1623, 1659, 2071, 2175, 2267] [Deservedly so.—Ed.] Pain and severity of inflammation were the guiding features of an exercise program, but early use of active exercises was advised.[1173] Weight bearing was not resumed until the patient could hold the knee firmly in full extension by active muscular power.[1658]

Difficulties in assessing results of some forms of physical therapy were discussed.[898, 1223] Various forms of *heat* therapy were nonspecific in approach, only symptomatic in effect, and empiric in dosage.[726]

Decreased eosinophil counts in 30 healthy volunteers following short-wave diathermy were thought to indicate an effect of nonspecific stress acting via the pituitary-adrenocortical system, and possibly to explain good results of such therapy in rheumatoid arthritis.[11] However, Moor[1472] thought that short-wave diathermy did not produce satisfactory muscular relaxation.

Ultrasonic therapy did not alter the course of rheumatoid arthritis, but resulted in symptomatic benefit in some cases.[726] The response to apparently uniform amounts of ultrasonic energy was variable; the dangers of promiscuous application were stressed.[53] Gersten found an increase in the relative water content of normal muscle and a decrease in hydration of normal tendon following the application of ultrasonic energy.[765] The effect of ultrasound on the extensibility of the tendon was attributed to "thermal denaturation of the protein of the tendon."[766] Current views of the physiologic responses of living tissue to ultrasonic energy were summarized.[1157]

Citrate *iontophoresis* improved exacerbations in small joints of the hands in 13 of 15 patients.[444] [Plain galvanism was used as a control; treatment was given for four weeks.—Ed.]

Occupational Therapy. More widespread recognition of the value of this modern form of remedial exercise,[2267] an essential component of rehabilitation,[146] was urged.[963, 1430] [The accent in recent years has been on occupational therapy which stresses restoration of purposeful function. This form of therapy has thus assumed a more important role in the attainment of successful physical rehabilitation.—Ed.]

Spa and Climatotherapy. A nationwide decline of spas was noted. However, properly conducted health resorts could combine the advantages of change of climate and environment with the modern broad concepts of physical medicine and rehabilitation.[1160] There was a need for tests to measure the degree of effect and to determine which patients will be benefited by climatotherapy.[963] [We agree.—Ed.] An interesting historical account of balneotherapy and massage was included in a discussion of early medicine in Japan.[1434]

Nonsurgical Orthopedic Measures. Indications and technics for use of casts, braces and splints were discussed.[246, 640, 1124, 1176, 1595, 1623, 1658, 1997] [Comments apparently were based on the authors' experiences, but were generally given as opinions, without supporting data.—Ed.] Stiffness was more likely to result from persistent activity of the disease than from short periods of immobilization.[1623] Conservative measures

were preferred when possible.[265, 1430] Basic principles of prescribing various braces for the hands were discussed.[2148]

Reported technics included: a weekly change of knee cast, which improved position without significant discomfort;[1173] change of casts every 72 hours to correct deformities of the foot,[1430] wax impressions of the feet, which allowed each metatarsal to seek its own level in a weight-bearing position;[1499] plaster encasement of metatarsal to allow weight-bearing in preference to rest in bed;[1125] support for more effective exercise of the hip,[1430] and mild elastic traction to maintain a position of function of the hand before contractures could become fixed.[297]

Manipulation was deferred until as much motion and strength as possible could be obtained.[1480] [The use of force in rheumatoid joints is inadvisable, and often causes exacerbation of symptoms and loss of motion.—Ed.] Failure often was attributed to muscles too weak to maintain straightening after it had been accomplished.[963] Daily exercises and passive stretching were more satisfactory than was the use of wedge casts, but manipulation with or without capsulotomy was indicated for correction of mild or moderately severe deformities of relatively recent origin without significant bony changes.[1659] Adrenocortical steroids and corticotropin were not of particular value as adjuncts to manipulation.[1422, 1623] [We do not agree.—Ed.]

Surgical Orthopedic Measures. The "peculiar problem in surgery of rheumatoid arthritis is the difficulty of foretelling with any accuracy the subsequent course of the disease."[111] The mental attitude of the patient also was considered to be important.[246, 310, 1430] Limited objectives were recommended.[265] Adrenocortical steroids and corticotropin were a therapeutic tool of primary importance to the surgeon.[1658] Among the corrective surgical procedures, arthroplasty was the most effective in accomplishing relief of pain and restoring mobility, stability and function,[1430] but results depended upon efficiency of muscles as well as shaping of opposing ends of bone;[310] extensive preoperative and postoperative muscle training was advised.[265, 1176] Better understanding of biochemical factors was needed in order to use metal or plastic prostheses more effectively.[1430]

Knee. Eleven of 33 operative procedures for rehabilitation of lower extremities were performed on the knee joint.[265] Satisfactory results occurred in nine of 11 totally disabled patients who had reconstructive surgery on 18 knee joints while under treatment with adrenocortical steroids or corticotropin.[1658] For flexion deformities, capsulotomy was more satisfactory than merely lengthening hamstring tendons.[1658]

Synovectomy was employed to preserve articular function. Short-term results were dependent upon the condition of articular surfaces at the time of operation; long-term results were determined mainly by the subsequent course of the rheumatoid arthritis.[1292] [Some of us have not had good results. The final place of this procedure will require further study.—Ed.]

Arthrotomy and lavage produced satisfactory decrease in activity of the disease in about 50% of patients.[1623] [Duration of relief was not stated. This needs to be confirmed.—Ed.] Insertion of a polythene sheet into the region of the suprapatellar pouch to prevent adhesions of the quadriceps in front of the femur was suggested.[1623]

Arthroplasty was indicated only infrequently.[1623] Nylon arthroplasty was preferred over fascia, and shortening of the tibial tubercle to tighten the extensor apparatus was helpful when indicated.[1430]

Insertion of a patellar prosthesis was less successful in rheumatoid arthritis than in degenerative joint conditions.[1410] [See Osteoarthritis.—Ed.] A stainless steel prosthesis fixed to the reshaped lower end of the femur converted the knee into a single

anteroposterior hinge and was reportedly successful six months after its insertion in one patient.[1384]

Hip. Results from arthroplasty were best when the muscles and bones were in good condition,[1623] but it was still only a procedure of last resort for carefully selected patients with the potential for successful rehabilitation.[1425, 1426, 1846] Steel or vitallium prostheses were preferred.[111, 1430] Only five patients with rheumatoid arthritis were included among 106 patients subjected to 110 nylon arthroplasty replacements at the hip joint; results were generally unsatisfactory.[1321] In another series, only four of 40 patients treated by 45 arthroplasties had rheumatoid arthritis; complications were stressed.[1426]

Among 47 operative procedures for rehabilitation of the lower extremities in 33 patients, operations were performed on the hip or adjacent structures 36 times. Arthroplasty of the hip was done 26 times, obturator neurectomy four, osteotomy three and adductor tenotomy three. With vitallium cup arthroplasty, motion was appreciably increased in only four of 20 patients.[265]

Hand and Wrist. "Good results" in all of 12 patients [895] and improvement in "about 70% of the patients" [297] were reported from correction of muscular imbalance and tenotomy or shortening of the metacarpals. Surgery was advised only for "burned-out" cases.[895] [We need more precise criteria for this often used category.—Ed.] Arthroplasty of the metacarpophalangeal joints was rarely necessary or successful. A painful deformed wrist was most effectively treated by arthrodesis.[1623] Technics for digital arthroplasty of the proximal interphalangeal joint were described.[344, 471]

Rehabilitation in Rheumatoid Arthritis. Rehabilitation entails reversal of crippling or physical decompensation within limitations imposed by disabilities.[1313, 1438] Factors important in successful rehabilitation in rheumatoid arthritis were discussed.[1310, 1313, 1401, 1659, 2267] The time required was generally less than that for patients with severe poliomyelitis or quadriplegia.[1313]

During a three-year comprehensive study of the rehabilitation potential of 38 rheumatoid patients (18 severely disabled), 22 became self-sufficient (eight with jobs outside the home), and 12 patients became partially self-sufficient. Four still required custodial hospital care, though some improvement in function had occurred.[1313] The experience of this special research group established at the Goldwater Memorial Hospital in New York City to study the rehabilitation of rheumatoid arthritic patients was the basis for several other reports.[1306, 1308, 1311, 1312] [Details and future assessment of the results are worthy of careful scrutiny. More detailed analysis of costs involved would be of interest.—Ed.]

Rehabilitation is a continuing process which can be started early with physical therapy to maintain joint function.[1891] Functional improvement should be the primary goal, rather than complete relief of discomfort.[1019]

Mobile Physical Therapy Services. The origin of mobile physiotherapy units was a response to a need to provide patients who were unable, because of their condition, to leave their homes to attend the physiotherapy department of a hospital.[1245] The pioneering of this new medical service in Great Britain began in 1919 and has extended into various communities in that country under the sponsorship of different charitable groups. The method of operation of some of these units now in operation in 33 centers was reported.[46] Jeeves listed the equipment used in the Leeds unit.[1035] [For those patients who cannot be hospitalized or are too severely afflicted to travel to a hospital as regular outpatients, physical therapy provided in the home has been a major advance. The Canadian Arthritis and Rheumatism Society has established 70 mobile units, and 20 such units

are operating in the United States under the sponsorship of the Arthritis and Rheumatism Foundation.—Ed.]

Rheumatoid (Ankylosing) Spondylitis

Archeologic studies have shown that ankylosis of all or part of the spine occurred in vertebrates millions of years ago. However, lesions of ankylosing spondylitis in man cannot be traced back very far. Skeletons unearthed in Egypt and Nubia showed ankylosis of some spinal segments but not of sacro-iliac joints.[2198] The description of the earliest known skeletal specimen of rheumatoid spondylitis was credited to Bernard Connor.[196, 2198]

Terminology. The term "ankylosing spondylitis" was considered unsatisfactory and not truly descriptive because the original meaning of the term was "crooked or angular," whereas now it implies union or adhesions, with immobility of joints. "Pelvospondylitis ossificans" was preferred by Romanus and Yden on the grounds that this designation better fits essential characteristics of the disease. "Pelvo" indicated the initial localization in sacro-iliac joints; "spondylitis" suggested that paravertebral ossification resulted from involvement of all spinal elements; "ossificans" signified the characteristic final phase of ossification or calcification.[1764] [But ossification does not occur in all patients with rheumatoid spondylitis.—Ed.]

Some rheumatologists adopted the view that rheumatoid (ankylosing) spondylitis and rheumatoid arthritis were distinct entities.[88, 908, 1987] Whether they are cannot be decided finally until more is known about their causes. In the meantime, it was considered best to regard both as unsolved problems.[196, 908]

Wide experience with veterans and civilians indicated to one writer that the medical profession as a whole was still not well enough acquainted with ankylosing spondylitis, and that early manifestations of this condition were often overlooked.[88] [We agree.—Ed.]

A study of prevalence of rheumatic disease among the population of several villages in North Holland showed that four persons among 3,378 more than 14 years of age (1,595 men and 1,783 women) had rheumatoid spondylitis. This number constituted 0.6% of 621 "complainers" and 0.1% of the total number.[493]

Rheumatoid (ankylosing) spondylitis was again found to be a disease primarily affecting young adults. The incidence by sexes was nine to 10 males to one female.[84, 1647] The course could be relatively mild in women [but not necessarily.—Ed.]; consequently, in some instances rheumatoid spondylitis has been mistakenly designated "osteitis condensans ilii." Thus, presently accepted ideas concerning the relatively high incidence of spondylitis among men may prove to be in error.[2087] [The relationship, if any, of osteitis condensans ilii remains unknown.—Ed.]

Hereditaty Factors. A high familial incidence was again reported. In one family the father, a daughter and a son were affected;[1861] in another family five members—three brothers, a sister and a paternal uncle—suffered from the disease.[1025] Roentgen studies of relatives of patients with rheumatoid (ankylosing) spondylitis were advised.[908] Among the families of 50 persons with ankylosing spondylitis, secondary cases were discovered in seven of 297 relatives; in a control series, only two instances were found among 2,932 related subjects.

Rheumatoid (ankylosing) spondylitis appeared to be inherited as a single autosomal factor with 70% penetrance in men and 10% penetrance in women. Heterozygotes or susceptible individuals were said to number six in 10,000 persons in the population of the United States.[1991] Penetrance was almost complete in both sexes in sibships including affected women, particularly in instances where a mother was found to have rheumatoid spondylitis.[1987]

Other Etiologic Factors. *Infection.* The hypothesis suggesting that genitourinary infection played an etiologic role in rheumatoid spondylitis was poorly supported.[2198] Only four of 21 patients with arthritis following urethritis (nonspecific and gonococcal) were found to have rheumatoid spondylitis.[699] A study of 117 patients with "pelvospondylitis ossificans" reportedly showed a very high incidence of preceding genitourinary infections. Spread either by way of lymphatics or blood vessels, or through contiguous tissues, was thought to be responsible.[585, 1765] [Although bacteriologic studies were reported, details were meager; it is difficult, therefore, to evaluate this study. One of us (D. C. G.) considers that some cases of rheumatoid (ankylosing) spondylitis are etiologically related to lower urinary tract infections.—Ed.]

Trauma. Trauma could not be identified as an important factor accelerating rheumatoid spondylitis. Very few persons with this condition came before a Workmen's Compensation Board, either because individuals with this ailment were not engaged in heavy work, or because back strains occurred less commonly in persons with fusion of the spine.[1397] In 10 of 68 patients the diagnosis was not made until symptoms had been present for more than 10 years. Severe trauma was sustained about the time of onset in six.[84] [The weight of evidence is heavily against trauma as an etiologic factor.—Ed.]

Literature concerning the coincidence of tuberculosis and ankylosing spondylitis was reviewed. Among 84 adult male patients in a sanatorium for tuberculosis, five also had rheumatoid spondylitis. In four, the symptoms of spondylitis preceded those of tuberculosis for from two to 10 years. In the other one, backache appeared six months after the patient had been admitted to the sanatorium. A high incidence of respiratory infections was also noted, and the prognosis in regard to tuberculosis was less favorable among such patients.[845] [There is no good evidence that tuberculosis is a factor in the pathogenesis of rheumatoid spondylitis.—Ed.]

Among children with rheumatoid arthritis, 80% showed either clinical or roentgen evidence of spinal involvement. However, calcification of paravertebral ligaments was noted in only two of 71 patients. Although females predominated over males (2:1) in this series, spondylitis occurred with equal frequency in the two sexes. Peripheral joints were involved in all. In none was spondylitis present alone.[99] [The high incidence of spinal involvement associated with peripheral joint disease in juvenile rheumatoid arthritis needs emphasis, but this is not necessarily synonymous with rheumatoid spondylitis.—Ed.] It was also reported that persons suffering with traumatic paraplegia sometimes show roentgenographic findings similar to those of rheumatoid spondylitis.[196]

Clinical Data. Usual symptoms and signs of rheumatoid (ankylosing) spondylitis were reviewed.[84, 88, 196, 363, 585, 781, 908, 909, 1647, 2198] Symptoms were intermittent rather than persistent at the onset, and were sometimes (erroneously) attributed to trauma. Pain developed insidiously in more than 75% of the cases, and appeared abruptly in less than 25%. Characteristically, pain was located in the lower portion of the back, across the sacrum or in gluteal regions, with or without radiation into the thighs. Pain usually was worse on first arising in the morning or after rest, and frequently was associated with stiffness. Pain simulated that associated with muscular spasms, and was described as a

"catch" or "lumbago" or as a stiffness with dull pain on movement. Sharp, lancinating pain, radiating into the thigh, abdomen or chest, as in patients with involvement of spinal root segments, was noted by some patients. Alternating or bilateral sciatica was the initial symptom in at least 10% of the patients. Later, pain was also noted in the lumbar, dorsal and cervical regions.

Characteristic signs included limited motion of the spine (especially hyperextension), loss of normal lumbar lordosis, fixation of the thorax in expiration, tendency to flexion deformity of the thoracic spine, and forward projection of the head. In addition, tenderness was noted over bony prominences, including ischial tuberosities, iliac crests, greater trochanters, margins of calcaneal bones, and plantar aspects of heels, and occasionally over the sacrum and vertebral spinous processes. A rounded stoop of the thoracic spine resulted in loss of height. Mobility of the spine was preserved in some patients. However, late in the course of the disease, ankylosis of the spine may become complete.[363, 908, 909, 1647, 2198]

A history of involvement of peripheral joints was obtained in as many as 50 to 60% of the cases, but in only approximately 25 to 30% was there sustained peripheral joint involvement. Hips, knees, shoulders and, less frequently, small joints, including those of the hands, wrists and feet, were most often affected. Involvement of peripheral joints preceding spinal symptoms was noted in 10 to 25% of the cases.[196, 585, 1485, 1647] Morrison suggested "having the sacroiliac joints x-rayed in any atypical arthritis in a young subject."[1485]

Chest expansion decreased early in the course of the disease, although the decrease was not usually evident until the thoracic spinal segments and costovertebral articulations became involved. [Some of us believe this is a late, not an early feature of this disease.—Ed.] Ribs became fixed in the position of expiration, and breathing was mainly of the diaphragmatic type. Remarkably little related cardiac or respiratory illness has been observed.[196, 363, 909] Total lung capacity and vital capacity are generally decreased, but residual volume remained approximately at the mean normal value. These findings indicated that decreased vital capacity was attributable to a limitation of ability to expand the chest. Dyspnea was seldom noted. The combination of a moderate reduction of maximal breathing capacity with a normal intrapulmonary mixing value suggested that patients with rheumatoid spondylitis do not suffer from emphysema.[1759]

Iritis was reported in from 8 to 50% of patients. Occasionally this symptom appeared before any symptoms of spinal involvement.[196, 585, 795, 908, 909, 1485, 1581, 1647, 1879] The incidence of iritis increased as the number of "observation years" increased.[908, 909] Of 322 patients with "primary" uveitis, 66 (20%) were believed to have an associated collagen disease. In this group, 28 of the males and six of the females had rheumatoid spondylitis, five had experienced an episode of rheumatic fever, and 27 had rheumatoid arthritis.[145] Rheumatoid spondylitis was suspected when a patient was "unable to advance his chin to the support of the slit lamp."[795] Scleromalacia perforans was not observed in association with rheumatoid spondylitis.[908] [Ophthalmologists should become more aware of the implication of iritis, especially in young men. At the Karolinska Hospital in Stockholm, Sweden, 40% of the arthritis patients seen routinely in the eye clinic are found to have spondylitis (I.F.D.).—Ed.]

Of 100 consecutive unselected patients suffering with rheumatoid spondylitis, four had psoriasis. The incidence of psoriasis in the general population was said to be 0.3%. Thus the association of psoriasis and rheumatoid spondylitis appeared to be greater than would normally be expected, and comparable to that reported between psoriasis and rheumatoid arthritis.[693]

Carditis and aortitis with aortic valvular insufficiency were reported in association with ankylosing spondylitis.[792, 1485, 1647] Other valvular lesions were noted in some instances, as was pericarditis.[196] [There is increasing evidence that there is a form of cardiac and aortic disease peculiar to rheumatoid spondylitis. The major manifestations are aortic insufficiency, conduction defects, anginal pain, pericarditis and cardiac enlargement.—Ed.] Urethritis was observed in five of 68 patients with rheumatoid spondylitis; in two it was reported as a forerunner of articular symptoms. Gonococci were not found in the urethral secretions. Four of the five patients with urethritis also showed involvement of peripheral joints.[1485]

Spontaneous dislocation of the atlanto-axial joint resulted in quadriplegia in a male patient with rheumatoid spondylitis. High cervical cord decompression by means of laminectomy followed by fusion was successfully carried out.[1350] An instance of fracture of the cervical spine occurring in a patient with complete ankylosis was reported.[61] A "poker back" may be found in persons with fluorosis, as well as in those with rheumatoid spondylitis. Increased bone density observed in roentgenograms of persons with fluorosis generally distinguished the two conditions.[1999]

The incidence of pulmonary tuberculosis was believed to be increased among patients with rheumatoid spondylitis. Of 184 patients with rheumatoid spondylitis, seven were found to have active pulmonary tuberculosis (five with active parenchymal disease and two with pleural effusions). In addition, two patients showed signs of quiescent pulmonary tuberculosis. In the same group, 21 showed evidence of peptic ulcer.[909] Another report also associated rheumatoid spondylitis with both tuberculosis and peptic ulceration.[1485] [The significance of hormone therapy in these patients was not discussed. The correlation noted may reflect an outcome either of excessively high doses of steroids or of unusual predisposition among the patients reported.—Ed.]

Laboratory Data. The sedimentation rate was normal in 19% of patients with rheumatoid spondylitis regardless of duration, extent or apparent degree of activity of the disease. Normal findings were observed in an even higher percentage of the cases when the studies were made early in the course of the disease. When sedimentation rates were found to be elevated, the rates were usually only slightly or moderately increased. Rarely, very high rates were observed.[1647] A linear correlation between sedimentation rates and fibrinogen levels was found.[1000] In a study of 70 patients, low serum albumin values were observed in 20%, elevated globulin values in 33%, and a low albumin/globulin ratio in 37%. Various flocculation tests (ammonium and zinc sulfate, colloidal gold, thymol turbidity and flocculation) showed changes considered to be nonspecific in character and similar to those associated with severe chronic infections.[909]

In contrast to the serum of patients with peripheral rheumatoid arthritis, that of patients with rheumatoid spondylitis without peripheral joint involvement usually gave a negative hemagglutination test.[26, 939, 2044] [The low incidence of positive tests in this disease, even in the presence of peripheral joint involvement, may be used as evidence that rheumatoid arthritis and rheumatoid spondylitis are divergent diseases. The incidence of positive tests is also low in *children* with peripheral rheumatoid arthritis. In this case, however, it is not used as an argument for a different disease. In a recent summary of 318 cases of rheumatoid spondylitis reported in the literature, 12 gave positive tests (about 4%). When peripheral joints also were involved, 63 patients (27%) had positive tests.[2289] Results with the recently introduced latex fixation test were comparable. See also section on Laboratory Studies in Rheumatoid Arthritis.—Ed.]

Zone electrophoretic analyses of proteins among patients with rheumatoid (an-

kylosing) spondylitis and rheumatoid arthritis revealed in both conditions a moderate increase in fibrinogen and gamma globulin levels, a corresponding reduction of albumin, and no significant alterations in levels of alpha and beta globulins.[1000] Other studies showed increased levels of alpha, beta and gamma globulins, also of polysaccharides associated with globulins. Most marked increases were noted in levels of alpha-2 globulin. Both serum proteins and polysaccharides tended to resume normal levels with clinical improvement of the patients.[1179] Notable variations were observed in complement activity of blood.[1106]

Studies of excretion rates of 17-ketosteroids, by 24-hour urinary assays and by fractionation studies of urinary extracts, resulted in normal findings.[1650] Normal fluoride concentrations were found in ribs, sacrum, ilium and vertebra, and in adhering soft tissues at postmortem, in a subject with rheumatoid (ankylosing) spondylitis of 10 years' duration.[1999]

Roentgen Features. Roentgenographic changes in sacro-iliac and apophyseal joints were reviewed, as were characteristic findings of calcification of intervertebral ligaments with "bamboo spine" appearance.[88, 196, 363, 585, 908, 1647, 1764, 2198] The earliest roentgenographic findings included lesions in upper portions of the sacro-iliac joints, giving the bones a ground-glass appearance, with poor marginal definition. Cancellous bone adjacent to the sacro-iliac joint later was found to be sclerotic, and irregular osteoporotic or cystic areas were observed in subcortical zones. Articular margins became irregular and sometimes appeared to be widened. Often bony "bridges" appeared to form across the joint space. Sclerosis and bony ankylosis with eventual obliteration developed eventually in most cases. Apophyseal joints might be similarly but less consistently affected. Paravertebral calcification generally was observed only after sacro-iliac and apophyseal changes developed. Osteoporosis of the vertebral bodies was noted early in some instances, but generalized osteoporosis occurred in only approximately 30% of patients, and was usually a late manifestation. Also noted were irregular margins of bones, "whiskery outgrowths," "bitten out" areas and osteoporotic lesions on outer aspects of the pelvis, ischial tuberosities, iliac crests, vertebral bodies, humeral heads and sites of tendon insertions.[908, 1764]

Romanus and Yden reported that spinal ossification was secondary to "anterior spondylitis." The initial phase was said to be characterized by superficial destruction of bone of the anterior surface of vertebral bodies near the upper and lower margins. This resulted in a loss of concavity on the anterior surface and to "squaring" of vertebral bodies. So-called "syndesmophytes" on lateral aspects of vertebral bodies were believed to be preceded by similar superficial destructive changes. This initial inflammation, decalcification, bone resorption and destruction are followed by a reparative phase of calcification, ossification and reconstruction. Filling-in of the normal cavity on the anterior surface sometimes brings about a return to the normal shape of the vertebral body. The destructive phase involving lateral surfaces of vertebral bodies is difficult or impossible to demonstrate by x-ray. Frontal views of the dorsal and lumbar spine later show bony outgrowths or syndesmophytes near vertebral body margins. Early lesions of the dorsal spine appeared to be destructive lesions of the anterior surface of the vertebral bodies, often best visualized in profile. Later they appeared as areas of ossification. The first costovertebral joints, visualized in the frontal view of the thoracic inlet, often showed ossification as an early finding. Spinal ossification was considered to be a sign of healing.[635, 1764]

Rheumatoid (ankylosing) spondylitis with involvement of sacro-iliac joints alone was differentiated from osteitis condensans ilii.[1748, 1856, 2087, 2174] Osteitis condensans ilii in eight males in a series of 20 cases was considered to be unusual because in the

past this radiologic abnormality has been said to occur almost exclusively in women.[1856] In another group of 20 patients with presumed osteitis condensans ilii, oblique views of the sacro-iliac joints of seven patients showed minimal but definite erosions of the joint margins, with patchy submarginal osteoporosis and irregular widening of joint spaces. These seven were believed to have ankylosing spondylitis.[2087] [Osteitis condensans ilii is a poorly described and little understood condition, and may be the basis of diagnostic error in rheumatoid spondylitis. Long-term follow-up studies of patients with these dense sclerotic changes involving only the iliac side of the sacro-iliac joint are needed. Further discussion of osteitis condensans ilii will be found in the Section on Backache.—Ed.]

Roentgenographic findings of rheumatoid (ankylosing) spondylitis were contrasted with those of crippling fluorosis. This condition, caused by absorption of excessive amounts of fluorides, showed radiologic findings including osteosclerosis, exostosis of long bones and, in some instances, areas of osteoporosis. In time all bones were involved, although the condition revealed a predilection for flat bones, including the pelvis, jaw and especially the lumbar vertebrae. Eventually the vertebrae were fused and spinal ligaments calcified. Increased bone density appeared to "obliterate" the sacro-iliac joints.[1999] [Differential diagnosis with the aid of roentgenograms should not be difficult.—Ed.]

"Physiologic" calcification or ossification of vertebral ligaments associated with decreased mobility of the spinal column was described. This condition needed to be differentiated from rheumatoid spondylitis, although it occurred in aged individuals without symptoms or signs of rheumatoid spondylitis. The region involved ranged from one or two vertebral interspaces to the entire spine. The dorsal spine almost always was involved if either the lumbar or the cervical segments showed these changes. The calcified ligament varied from 5 to 10 mm. in thickness, often appeared lax or too long for the intervertebral spaces, and lay anterior to and distinct from anterior margins of vertebrae to which this ligament was attached. Osteoarthritic changes affecting sacro-iliac joints and spine sometimes were associated with this lesion.[1934] Radiologic changes progressed relentlessly in some of 121 patients with rheumatoid spondylitis who appeared to have little discomfort and in whom functional ability could be nearly normal after 11 years' follow-up.[636]

Pathology. Pathologic findings in ankylosing spondylitis have been described as nonspecific inflammatory changes similar to those occurring in diarthrodial joints in rheumatoid arthritis. Calcification of the annulus fibrosis of intervertebral discs and calcification of paravertebral ligaments were considered to be one phase of this process.[196, 908, 1350] [Reviews of reports previously published and based on a limited number of tissue examinations appeared in several papers, but little in the way of new information was reported. There is need for further investigation in this area.—Ed.]

Gross autopsy findings on the skeleton of a patient who had both complete ankylosis of the spine and ankylosis of practically all peripheral joints were reported. Histologic studies were not included.[782] Histologic studies based upon 19 biopsy specimens and an autopsy performed on a patient with ankylosing spondylitis showed good correlation between radiologic and histologic findings. Sites of biopsies included spinous processes, iliac crests, acromioclavicular joints, hip, sternal synchondrosis and an intervertebral disc. Vertebral joints from the autopsied case were examined. Endarteritis obliterans of vessels adjacent to bone and inflammatory changes in the soft tissues in most specimens were seen. Edema, round cell infiltration and endarteritis in the alveolar tissue were found in sections from the intervertebral disc. The acromioclavicular joint showed irregular destruction of bone and articular cartilage, with granulation tissue and

new bone formation. In other areas, cartilage was of normal thickness but superficially frayed. Synovial membranes were edematous and showed sclerosis in some areas, and increased vascularity with infiltrations of lymphocytes, plasma cells and leukocytes in others. Eosinophilic leukocytes and areas of fibrinoid necrosis were not present.[635, 1764]

Synostosis between the manubrium and body of the sternum is not a senile change. This condition was regularly present after the fourth decade of life and was described as either a primary or "matrical" synostosis due to obliteration of a primary cartilaginous joint during early life, or a secondary "sclerotic" synostosis due to a pathologic obliteration of a secondary cartilaginous joint during adult life. The primary type was three times more frequent than the secondary, sclerotic type.[68]

Diagnosis. Although early recognition of rheumatoid spondylitis may be difficult, heightened interest and suspicion of the possibility on the part of the physician should result in a shortened period between onset of symptoms and establishment of the diagnosis. In young adults, recurrent episodes of low back pain with or without sciatic radiation, together with morning stiffness and pain in intercostal regions, should lead one to suspect rheumatoid spondylitis. Also suggestive of this condition is a history of peripheral joint involvement in such patients. The findings of limitation of spinal motion, decreased chest expansion and positive "straight-leg raising" tests are further suggestive of the presence of this disease.[84, 88, 363, 585, 1647] [These clinical features, where confirmed by characteristic roentgenographic findings, make certain recognition possible. See Clinical Data, this Section.—Ed.]

Differentiation from osteitis condensans ilii, a condition said to occur almost exclusively in women, rested on proper interpretation of roentgenograms. In osteitis condensans ilii the sacro-iliac joints show neither narrowing nor irregularity, although the ilium adjacent to the joint appears to be sclerotic and dense.[1856, 2087] [Osteitis condensans ilii is primarily a roentgenologic diagnosis. See Roentgen Features, this section.—Ed.] In crippling fluorosis, roentgenograms show marked osteosclerosis of vertebrae in addition to ligamentous calcification. Except for density of bone, sacro-iliac joints appear to be normal in this condition.[1999] A skin test involving application of an ointment containing tetrahydrofurfuryl ester of nicotinic acid was said to be unreliable for detecting rheumatoid spondylitis.[2124]

Treatment. Objectives of treatment in rheumatoid spondylitis included prevention of deformity, relief of pain and maintenance of the patient's activity. Some patients were more interested in obtaining immediate comfort than in planning a long-range program.[781, 966, 1647, 2198] Exercises for the back, stretching exercises for the hamstring muscles and postural training, together with breathing exercises, were more effective than rest in bed, plaster casts and braces. Exercises needed to be planned individually, and a proper balance sought between rest and activity. Sleeping on the back on a firm mattress and avoiding the use of pillows if possible were advised.[585, 781, 903, 966, 1647, 2198, 2267] [Rest in bed, casts and braces often relieve symptoms and prevent deformities.—Ed.]

Roentgen Therapy. Writers again described roentgen therapy as effective for rheumatoid spondylitis. Relief of symptoms followed proper roentgen therapy

in from 50 to 80% of the cases.[88, 585, 908, 916, 966, 1134, 1606, 1875, 2005] The range of spinal movements generally was little influenced. However, motion improved somewhat among some in whom the disease was in an early stage.[908] Alleviation of pain and stiffness generally appeared within one to four weeks after completion of a course of treatment. But those with marked rigidity of the spine remained permanently disabled in spite of roentgen treatment.[361, 1647] Relief of symptoms was ascribed to a lessening of muscle spasm.[1647]

It has been implied that roentgen therapy acts as an acute stress stimulating the adrenal cortex. In this connection, a study of the effect of irradiation on Rhesus monkeys was of interest. Initially a rise was observed in plasma 17-hydroxysteroid levels. A peak was reached in from four to eight hours, and was followed by a fall to normal within 12 hours. Polymorphonuclear leukocytosis, eosinopenia and lymphopenia were also observed to last a few hours and return to normal within 24 hours. This effect was related to the dosage. Whole body irradiation with 800 roentgens proved fatal in every instance. Survival periods ranged from six to 17 days. A terminal rise in levels of plasma 17-hydroxysteroids together with pancytopenia was noted in all animals treated.[719] [This study of the nature of effects of radiation is noted because very little information is available concerning effects of roentgen therapy in rheumatoid spondylitis.—Ed.]

"Complete arrest" of the process was said to have followed roentgen therapy in some patients treated during the "prespondylitic" period, i.e., the period before bony ankylosis had developed in sacro-iliac joints and when symptoms were minimal.[2005] Whether roentgen therapy affects the natural course of rheumatoid spondylitis was not determined. [Previous studies have shown it does not.—Ed.] Relief of pain may last for weeks, months or years.[916, 2198] In one reported study, 275 of 332 patients considered to have rheumatoid spondylitis were given x-ray therapy. Best results were obtained among those whose symptoms had been noted for periods of less than five years and when roentgenographic changes were observed only in the sacro-iliac joints. Poor results were attributed to treatment of patients with conditions simulating rheumatoid (ankylosing) spondylitis, but not influenced by roentgen therapy.[1879]

Women patients should be warned regarding sterility, artificial menopause and temporary menstrual irregularities as possible complications of roentgen therapy for rheumatoid spondylitis.[966, 1647, 2005] A technic employing so-called "tangential fields" was thought to be effective in reducing the likelihood of damage to ovaries. Others believed that irradiation of sacro-iliac joints of female patients should not be carried out during the childbearing period.[966, 2005] Conventional roentgen therapy given 47 women caused permanent amenorrhea definitely in 13 and probably in another three. Thirteen of the 16 were under the age of 45.[1879]

Concern regarding all types of roentgen therapy has increased in recent years. Activation of quiescent tuberculosis and development of aplastic anemia were described.[1879] In a report from the Netherlands, five patients were observed with myeloid leukemia and two with aplastic anemia. Leukemia had been observed among patients with ankylosing spondylitis only after roentgen therapy. Since the incidence of leukemia in the general population was reported as 1:25,000, it seemed unlikely that the onset of leukemia was a chance occurrence. Intervals between administration of roentgen therapy and death were one year and two years for patients with aplastic anemia, and 10 weeks to six years for patients with myeloid leukemia. No relationship was observed between dosage and these intervals, although in the case of the patient with the shortest interval an unusually large dosage had been employed.[2134]

Data were reported on more than 9,000 patients with rheumatoid spondylitis treated by roentgen therapy at 37 centers throughout England, Wales and Scotland during the years between 1940 and 1954. Twenty-five patients were known to have developed leukemia (19 acute and six chronic). The diagnosis in two was lymphatic leukemia, in 14 myeloid leukemia, and in five monocytic leukemia; in four the type was not specified. This number was incomplete because follow-up was not possible in 44%. In four included patients, leukemia and ankylosing spondylitis were coexistent when the treatment was undertaken. This occurrence of deaths from leukemia was at least five times and possibly as much as 10 times as high as that expected for this group. Among patients who received more than one course of treatment, fatal leukemia occurred approximately nine times more often than expected. It was suggested that patients with ankylosing spondylitis are unusually susceptible to leukemia, and that the incidence of leukemia is higher among patients who receive more than one course of x-ray therapy. This study suggested that some if not all instances of leukemia among these patients may indeed be attributed to x-ray therapy.[437] [These reports by van Swaay [437, 2134] indicate that the onset of fatal hematologic complications was due to x-ray therapy. Six additional deaths from leukemia in patients with rheumatoid spondylitis who had received radiotherapy have been reported.[953, 1879, 1756, 2134] At the 1958 annual meeting of the American Rheumatism Association, one of us (D. C. G.) reported five deaths from acute myelogenous leukemia in a group of 146 patients with rheumatoid spondylitis treated with roentgen therapy. There were no cases of leukemia in 445 patients with rheumatoid arthritis not treated with roentgen therapy. At the same meeting Frohman, Silberberg and Duff reported four cases of leukemia and one case each of Hodgkin's disease and agnogenic myeloid metaplasia from a group of 466 patients with rheumatoid spondylitis treated with x-ray therapy. These two recent studies strongly suggest that the incidence of leukemia is greatly increased in spondylitis patients receiving x-ray therapy. These observations are not surprising in view of the well recognized hazard of effects of radioactivity on blood-forming organs in other diseases. Although x-ray treatment is one of the most reliable means of combating the discomfort and pain in rheumatoid spondylitis, its use must now be considered in light of the increased incidence of leukemia. No statistical analysis of this problem has yet been feasible because data have been insufficient; it would be helpful if further instances of leukemia and aplastic anemia appearing after roentgen therapy could be reported.—Ed.] One writer expressed the opinion that roentgen therapy shortens the life span, and that either leukemia or other complications occur with such high frequency that this type of treatment ought to be abandoned.[2198]

Phenylbutazone. This drug was thought to be more effective for rheumatoid spondylitis than for the peripheral type of rheumatoid arthritis, and was considered to be especially helpful for patients with pain not relieved by aspirin, and for individuals with far advanced ankylosis. When tolerated, it was perhaps the most effective drug in the treatment of the advanced case. Those patients who did well on phenylbutazone for six months' therapy usually continued to do so over long periods.[164, 781, 916, 1327] For most patients, improvement was obtained from daily amounts ranging from 300 to 600 mg. Doses of 300 to 400 mg. per day were apparently less toxic than were higher doses. Results were said to compare favorably with those obtained from roentgen therapy.[164, 1327] [The toxic effects of phenylbutazone are discussed under the section on "Treatment of Rheumatoid Arthritis."—Ed.]

ACTH and Cortisone. These were described as effective in improving functional capacity of patients with ankylosing spondylitis. The objectives of therapy with compounds presently available should not be overambitious, since the effects are palliative and not curative. For some patients with spondylitis,

symptoms can be controlled better with either ACTH or cortisone than with any other treatment available.[263, 781, 916, 1581, 1647, 2049, 2199] [Dosage should be kept as low as possible. Problems regarding dosage, administration and management are the same for patients with spondylitis as for those with rheumatoid arthritis. See Hormone Therapy of Rheumatoid Arthritis.—Ed.]

Severe adrenocortical insufficiency was observed following manipulation of joints in a patient with rheumatoid spondylitis in whom cortisone had been discontinued.[893] Concurrent administration of calcium phosphate, vitamin D and methylandrostenediol in connection with long-term ACTH and cortisone therapy was recommended as a means of counteracting osteoporosis.[684] [There is no good evidence that the osteoporosis can be counteracted this way.—Ed.] Administration of either ACTH or cortisone was said to be justified only in the most severe cases of rheumatoid spondylitis.[2199]

Surgery and Other Measures. Osteotomy of the spine and other surgical procedures were indicated to correct marked deformities in certain carefully selected cases.[111, 2005] Dextroamphetamine sulfate was employed as an adjunct to other therapy because of an antidepressant action. Results were good in some but unimpressive in others.[94]

Course and Prognosis. For most patients with rheumatoid spondylitis the socio-economic and functional prognoses are good.[1647] In spite of progressive deformity, functional ability—that is, ability to make a living and to care for a family—is not seriously affected in most instances.[196, 636, 1647] A follow-up study of 121 patients showed that 76% were working full time.[196] Only five were invalided. A period of rapid progression of physical and radiologic signs had occurred early in the course of the disease in many instances. Later, functional capacity frequently improved, even though roentgenographic findings continued to progress. Functional ability was poorly correlated with deformity, since patients who were severely deformed were often capable of considerable physical activity. Involvement of shoulders and hips indicated a poor prognosis. Although the disease became arrested in some, it progressed slowly in a majority of the cases. A study of 274 patients with spondylitis whose histories were followed for periods ranging from one to 20 years indicated that fatalities were not more frequent during this period than would be anticipated for normal persons. Longevity was not affected. The causes of death were determined in seven cases: three had died of heart failure from valvular heart disease; one died following an appendectomy; another died following an injury, and one died of carcinoma of the lung.[196]

Osteoarthritis (Degenerative Joint Disease)

Definitions. Previous definitions (Eleventh Rheumatism Review) were reëmphasized;[413, 1284, 1648] spurs from ossification in tendons, fascia and areas of periosteal elevation did not per se warrant a diagnosis of osteoarthritis.[413]

Incidence. Osteoarthritis was still regarded as the "commonest of the rheumatic diseases"[1307, 2013] and a "major cause of disability in the aged."[2175] Of 200 patients seen in private practice, 31.5% had osteoarthritis.[396] Osteoarthritis was found in 6.9% of 3,378 persons living in North Holland, and 37.7% (234 of the 621 persons in the group) had "some form of rheumatism."[493] Osteo-

arthritis was present in 894 of 4,654 persons (60% more than 60 years of age) whose preëmployment examination included x-rays of the lumbar spine.[1795] The incidence of idiopathic Heberden's nodes was found to be about 30% after the age of 70 in women.[1992]

Degenerative arthritis of the spine was the most common type of arthritis seen by the Workmen's Compensation Board of Ontario.[1897]

Arthritis of the knee was observed more frequently than was that of any other joint of the body.[1173] [No data were offered.—Ed.]

"Primary generalized osteoarthritis" described by Kellgren[1, 1112] occurred in 440 patients with osteoarthritis (almost one eighth of the total patients seen in the University Rheumatism Center at Manchester, England). A case satisfying all the criteria for this diagnosis, with the unusual feature of involvement of both sternoclavicular joints, was initially diagnosed as rheumatoid arthritis.[288] [The differentiation of primary generalized osteoarthritis from rheumatoid arthritis often is difficult, and the limits of each are not entirely clear.—Ed.]

Clinical Aspects. Osteoarthritis was considered to be a disease of aging rather than of old age[1284] and, in early stages, likely to be asymptomatic.[896, 1648] Later, "joint pain is directly proportional to activity."[1307] Clinical symptoms usually developed insidiously, as increased articular stiffness or transient aching after unusual physical activities. Classification into primary or secondary types was again emphasized; the secondary types included those resulting from trauma of obesity, posture or misuse of joints, ochronosis, hereditary defects, and other types of joint disease.

Cause of Symptoms. "Pain from osteoarthritis may result from tearing of tissues or hemorrhage, osteocartilaginous loose bodies or compression of the nerve,"[1648] fibrosis and shortening of the joint capsule, or vascular engorgement of subchondral bone.[1283, 1663, 2113] Obesity could adversely affect an already degenerated weight-bearing joint, but there was no definite causal relationship.[1283] Clinical manifestations paralleled pathologic changes developing as the disease progressed.[1480] [Mechanisms for production of symptoms from osteoarthritis continue to be largely theoretic, speculative, and restatements of previously reported opinions.—Ed.]

Special Locations. *Hands.* An intact nerve supply to the hand was considered to be essential to the development of "idiopathic Heberden's nodes,"[1993] and fingers affected with "traumatic Heberden's nodes" appeared to be immune to "idiopathic" changes.[1994] No relationship was noted between the occurrence of Heberden's nodes and obesity or hypertension.[1993] Genetic studies suggested that Heberden's nodes were not properly a part of a generalized osteoarthritis.[1989] Collins[413] concurred.

Heberden's nodes in identical female twins, age 68 years, were reported for the first time.[1990] The "not uncommon" and frequently overlooked occurrence of osteoarthritis of the first carpometacarpal articulation was emphasized.[71]

Recurring myxomatous cutaneous cysts on the dorsal surface of the fingers, usually in close proximity to and a little to the side of the distal interphalangeal joint, may be mistaken for a Heberden's node.[1007] [This uncommon condition, originally described as "synovial lesions of the skin," occurs on a finger or a toe. They may also be confused with outpouchings of synovial tissue containing viscous fluid. Also, Heberden's nodes may undergo degeneration and form gelatinous cysts containing hyaluronic acid.[1014] Pathologically, it represents a localized degeneration of the corium, the cause of which is unknown. Most of the reported cases have been in the dermatologic literature. Radiation

therapy usually effects a permanent cure. One of us (D. C. C.) considers these to be synovial outpouchings.—Ed.]

Temporomandibular Joints. Degenerative changes were initiated by unilateral pull of the external pterygoid muscle on the disc and pressure of the condyle on the richly neurosensitive loose connective tissue behind the disc.[1892] Hypermobility and disorders of bite predisposed to pain,[1638] but complaints often exceeded pathologic findings.[1842, 1985]

Hip. Osteoarthritis of the hip was the most painful and disabling form of osteoarthritis,[1534] and was caused or predisposed by various unrelated factors,[271] the common denominator of which was thought to be a "vascular calamity in the subchondral region of the joint."[1663] [These ideas are not new.—Ed.] Osteoarthritis of the hip joint was monarticular in only 25 of 100 patients.[1239] Effusion into the joint was rarely observed, and spontaneous bony ankylosis does not occur in osteoarthritis of the hip.[1012]

Spine. See *Osteoarthritic Spondylitis.*

Other Articulations. The ankle joint usually escaped damage, owing to the presence of that "admirable ball-bearing joint, the astragalus."[2071] Kuhns found the knee joint to be affected in at least one-half of the patients suffering from osteoarthritis.[1175]

Kellgren[1112] reported on further studies of "primary generalized osteoarthritis." (See Eleventh Rheumatism Review.) [Though the pattern of joint involvement was "remarkably uniform," the overlapping features of "generalized osteoarthritis" and "rheumatoid disease" still need further clarification.—Ed.]

Pathology. Several general reviews appeared,[410, 463, 1283, 1524, 1534, 2013] but possible systemic backgrounds have been less well defined than has the local nature of osteoarthritis.[413] That osteoarthritis might be a "vascular disorder" was restated[2113] and disputed.[1284]

The earliest and most essential changes mentioned were loss of elasticity of cartilage and reduction of the number of cartilage cells, but morphologic changes were found to be essentially the same, whatever the cause.[463] Cartilage found at the eburnated surfaces was thought to result from metaplasia of seams of osteoid in reparative tissue.[1727] Advanced changes in cartilage and some remodeling of bone were found in the knee at necropsy in about 25% of patients more than age 50, less frequently in the hallux and acromioclavicular joints, in the hip and elbow in about 10%, less commonly in the shoulders, and only rarely in the sternoclavicular joint.[413] Fibrocartilaginous loose bodies were formed in only two of 131 hip joints,[1284] but the acetabulum was found to be damaged in every patient with osteoarthritis of the hip.[419]

Cysts of the Hip. Cystic areas were regarded as foci of traumatic bony necrosis[1727] or fibrous remnants of vascular calamity of unknown nature.[1663] Cysts were found on x-rays of serial sections in each of 36 patients with osteoarthritis of the hip, but in none of the 14 patients with fracture of the femoral neck.[1727] [Landells (1953)[1] suggested that bone cysts in degenerative joint disease resulted from intrusion of synovial fluid under pressure into subchondral bone at sites of cartilage degeneration.—Ed.]

Synovial Fluid. Fletcher[695] found no essential difference in the mean degree of polymerization of hyaluronic acid as judged by limiting and anomalous viscosities in the synovial fluid of knees with osteoarthritis or rheumatoid arthritis. A higher mean value of specific viscosity in osteoarthritis was attributed to a higher concentration of hyaluronic acid in this condition.

Etiology and Pathogenesis. *Microtrauma.* Trauma precipitated the changes of osteoarthritis in tissue which could not adequately repair itself,[1239]

but the trauma was not known to be responsible for the initial chemical change.[463, 1397] Certain diseases and unknown factors associated with defective elimination of metabolites could result in ordinary function assuming the character of repeated trauma.[250] Loss of muscle tone, adaptive ligamentous changes, and consequent altered weight bearing were important contributing circumstances.[1301] Kellgren[1112] again regarded primary generalized osteoarthritis as largely unrelated to trauma.

Hormonal Factors. Endocrine deficiencies [not defined.—Ed.] were still considered to be one of the possible explanations for degenerative joint disease.[250, 670] A definite though unexplained relationship between idiopathic Heberden's nodes and ovarian function was postulated.[1993]

Heredity. Although both Heberden's nodes[1989] and "primary generalized osteoarthritis"[1112] might result from an inherited defect, the role of heredity in osteoarthritis has not yet been fully assessed.[1307] The mechanism of inheritance of Heberden's nodes seems to be firmly established as a single autosomal character, dominant in women and recessive in men.[1992] Hereditary influences are well understood in osteoarthritis of the hip and of the spine.

Other. Various mechanisms reiterated included: fibrosis and shortening of joint capsule,[1283] a vascular response in bone from fibrillation of cartilage,[2113] tearing of tissues or hemorrhage, osteocartilaginous loose bodies or compression of the nerves,[1648] anoxemia caused by local arteriosclerosis and deficient blood supply,[1239] and accumulation of destructive metabolites in or near joints.[250] [No evidence was cited.—Ed.]

"Despite much work there are still wide gaps in our knowledge of the metabolism of cartilage."[463] [We agree.—Ed.] The precise cause of osteoarthritis has remained obscure.[853] Clinical manifestations closely paralleled pathologic changes as the disease progressed.[1480]

Laboratory Data. C-reactive protein was absent in the synovial fluid in all of 14 patients with osteoarthritis and in 11 patients with "arthritis due to trauma."[337] Results of differential agglutination tests for rheumatoid arthritis were negative in "uncomplicated cases of primary generalized osteoarthritis." The sedimentation rate of erythrocytes was generally low, but some patients in the group had elevations to 60 mm. at one hour.[2206, 1112]

Roentgen Studies. Osteoarthritis was considered to be a clinical diagnosis; x-rays were not considered to be an adequate basis for the diagnosis[912, 1301] and were no measure of joint incapacity.[1307] Though there was a disproportion between x-ray findings and symptoms,[71, 209, 640, 1112] the findings on roentgenographic examination correlated closely with those on anatomic dissection and histologic study.[413]

Subchondral sclerosis seen in roentgenograms indicated severe cartilaginous damage rather than avascular necrosis; *flattening of the head* of the femur indicated that bony debris had entered the joint; a *bony ridge* on the under surface of the femoral neck indicated advanced disease and adduction deformity.[1284] Changes in the roentgenographically invisible articular capsule could be inferred from the manifest abnormalities of bone.[1283]

Roentgenographic signs of cysts in the head of the femur were found only when degenerative changes were advanced,[1284] and indicated that continued use of the joint had impeded the natural processes of repair.[1727]

The radiologic changes in 12 patients with acromegaly which had to be differentiated from osteoarthritis included: enlargement of vertebral bodies with

accretions of new bone; enlargement of apophyseal joints, and circumferential overgrowth of the heads of some metatarsals and metacarpals, resulting in an appearance of "mushrooming" of the shafts into the heads of the bones.[680] [This was a carefully conducted, reliable study.—Ed.]

Treatment. Aims of therapy were reiterated,[1177, 1344, 1648, 2013] with emphasis on an optimistic approach,[37, 1480, 1581] conservative measures,[866, 1177, 1480, 1648, 2013] and prophylaxis.[905] Therapy was generally symptomatic "because we do not understand fully the development of osteoarthritic changes."[1174]

For treatment to be most effective it was necessary to determine that symptoms were due to osteoarthritis, and for conditions which aggravated the osteoarthritis to be avoided or controlled.[1648]

Medical Therapy. Aspirin was an effective if not glamorous drug; little if any additive value was found in combined salicylate preparations.[1648] Salicylamide was not an effective analgesic.[114] Opinions regarding phenylbutazone varied from "the drug of choice,"[1581] "valuable,"[1239] and "most effective" analgesic[419] to "not routinely advised,"[1534] not justified for general use,[486] of doubtful value,[1648] productive of no striking relief,[955] and seriously toxic.[164, 665, 911] [A general discussion of the pharmacologic and physiologic action of phenylbutazone and its potential toxic effects is contained in the section on "Treatment of Rheumatoid Arthritis."—Ed.]

Use of vitamin B complex was frequently beneficial[1534] [no proof offered.—Ed.], but injections of B_{12} were ineffective.[2298] Diamphetamine sulfate was a useful adjunct.[94] [Improvement was "psychically motivated" and subjectively determined.—Ed.]

Benefit from systemic adrenocortical hormonal therapy in osteoarthritis was limited to a "general tonic effect," analgesia and increased muscular strength,[721] and use of adrenocortical hormones was not warranted for osteoarthritis except in local injections of hydrocortisone supplementing other therapy;[741, 1534, 1972, 2013, 2195, 2272] even this was rarely needed.[1648] Hormonal effects were variable,[1802, 2195] transient,[1174] symptomatic,[1724] and less beneficial than in inflammatory rheumatic diseases.[721] However, for some patients with synovitis and flares of osteoarthritis, relief from hydrocortisone given intra-articularly was more rapid, even if not prolonged, than would have been expected from other treatment.[2272] Pain was more frequently relieved than was swelling;[1802] relief was considered to be satisfactory if 50% or more of pain was relieved for three weeks or longer,[1480,2195] but prolonged use seemed unjustified,[721] and the injection therapy was not indicated to permit overuse of affected joints.[2272]

Implantation in the abdominal wall of 3 to 5 gm. of autoclaved placental tissue produced analgesia and "some subjective benefit" in 13 of 14 patients followed for about four years.[1272] Measurements of effects of various hormones in 14 patients with osteoarthritis by a thermal response test indicated that only cortisone produced significant results.[2252] [During the period covered in this review no remarkable progress has been made in the medical management of osteoarthritis. Many papers based upon uncontrolled observations and expressing unjustifiable benefits have not been included.—Ed.]

Physical Therapy. The value of physical therapy was again stressed,[521, 1174, 1472, 1535] emphasis was directed particularly to appropriate muscular exercise and

strengthening, and reëducation.[37, 87, 911, 1775, 2071, 2175, 2267] Appropriate articular supports were almost always part of the treatment.[37, 640, 1648] Use of ultrasound "improved" 67 to 85% of osteoarthritic patients in one series,[1839] only 30 to 35% in another series.[767] The physiochemical and biologic effects of ultrasound were reviewed.[569, 767, 1060, 1157, 1840] Ionization was of doubtful if any value.[2071]

X-ray Therapy. This has been most effective for the traumatic inflammation so frequently seen in osteoarthritis,[640, 1173, 1174, 1633, 1871] but now has been discarded [1480] and replaced by intra-articular injections of hydrocortisone.[1173] [Use not recommended.—Ed.]

Surgery. This was still advised only for increasing severity of the disease and intolerable pain,[866, 1480] and was rarely necessary.[1174, 1177, 1534]

Hip Joint. Severe handicap and intolerable pain [1846] in patients potentially capable of rehabilitation [310, 640, 1142, 1426, 1480] were given as the only valid reasons for arthroplasty of the osteoarthritic hip.

Cup arthroplasty and replacement of the femoral head with acrylic prosthesis were considered notable advances in surgical treatment of the hip,[1581] but results did not compare with those from use of the same procedures for fractures.[566] No significant differences were observed between results of cup arthroplasty and those obtained by using the Judet prosthesis,[1142] the acrylic prosthesis was both preferred [70, 419, 866] and not advised.[838] A solid nylon prosthesis was considered to be satisfactory in a study of 110 operative hip joint replacements.[1321] Compere summarized the factors which he considered in selecting a hip prosthesis.[420] Complications were stressed.[250, 1425, 1426] Better results were obtained from cup arthroplasty for osteoarthritis, especially when unilateral and when patients were relatively young males, than for rheumatoid arthritis.[1885] Good results were reported in 80% of 50 arthroplasties on 42 patients (80% in the sixth decade) followed from 12 to 45 months;[1846] results were "discouraging" in another series of 80 patients with osteoarthritis, although the use of cup arthroplasty led to a more favorable outcome than did the acrylic prosthesis.[507] "Uniformly satisfactory" results were reported from use of a MacMurray osteotomy, even though the rationale was "obscure and beneficial effects hard to explain." [1407]

Successful relief of pain was attributed to section of nerve fibers [1407] or complete extirpation of the capsule, this being the most certain method of complete denervation.[139] However, capsulotomy, obturator neurectomy [866] and denervation [1480] "have not worked out satisfactorily."

Arthrodesis eliminated need for crutches in all 17 patients using crutches preoperatively;[1480] this operation was described as "still the surgeon's sheet anchor in osteoarthritis whenever surgery can be justifiably considered." [111] Arthrodesis was considered to be a good operation in unilateral osteoarthritis in patients under 40 or 50 years of age.[1526]

Knee Joint. A hinge steel prosthesis which permitted flexion and preserved lateral stability was inserted in four patients, one of whom had prompt bony overgrowth; two of the patients had been followed for only three months.[1889] Patellectomy proved useful when osteoarthritis was most pronounced at the patellofemoral articulation;[1698] a vitallium patellar prosthesis permitted restoration of the quadriceps extensor mechanism in 10 patients followed up to five years.[1410] Denervation of the knee joint in two patients did not result in a Charcot's joint because only the inside of the joint was deprived of its nerve supply.[1239, 1240]

Other. Condylectomy rather than meniscectomy was recommended for the small group of patients with irreversible changes in the temporomandibular joint.[950]

Osteoarthritis of the Spine

Osteoarthritis of the spine was called "a popular and easy diagnosis" that "can be made all too readily to explain a large number of aches and pains."[912] Since there was no evidence of a "disease" process, natural osteogenetic responses should not be labeled "arthritic."[165] The terms "spinal osteophytosis"[245] and "deforming spondylosis"[183] were preferred. Vertebral osteophytosis was regarded as the terminal stage of disc disease or degeneration;[413, 1524] it would be therapeutically misleading if this term were considered to be synonymous with postural strain, vertebral compression or arthritis of the spinal joints.[166] [We agree.—Ed.] However, overlooking the neurologic syndromes caused by resulting compression of neural structures could lead to erroneous therapy.[1524]

Incidence and Etiology. Degenerative arthritis of the spine represented the greatest number of cases of arthritis seen by the Workmen's Compensation Board of Ontario, and also represented one of its most difficult problems in assessing responsibility. The aggravating but not causative effect of trauma on osteoarthritis of the spine was recognized.[1397] Osteoarthritis of the spine was "clearly related to age";[183] in particular, cervical spondylosis most often declared itself in the fifth to sixth decades,[353] was "a common disease in elderly people," and was an important factor in the pathogenesis of obscure lesions of the pyramidal tract.[1578] An unusual cause of cervical spondylitic myelopathy was congenital smallness of the laminae and spinous process of the axis. One such case was reported.[379]

Symptoms. Whether early, uncomplicated vertebral osteophytes could cause pain was disputable, but the high concentration of sensory nerve endings in adjacent ligaments supported the likelihood.[166] The principal neurologic syndromes caused by compression and chronic irritation of the neural structures were described.[586, 1524] Narrowed spinal canal and physical signs of involvement of the spinal cord were found in 25 of 50 patients more than age 50, and moderate or severe narrowing of the spinal canal due to posterior vertebral osteophytes was found in 34 of 38 patients; neurologic signs might precede symptoms, but evidence of compression of the spinal cord never occurred without moderate or severe narrowing of the spinal canal.[1578] Symptoms of osteoarthritis of Luschka's joints in the cervical spine resulted from excessive angulation, rather than compression, of the spinal nerve by osteophytes.[353] Long-standing and intractable cervical pain seemed more likely due to psychopathologic states than to organic lesions; detailed clinical evaluation in such instances was more important than was roentgenographic examination.[917] In an otorhinolaryngology practice, osteoarthritis of the cervical spine was found to be one of the causes for the common complaint of a "lump in the throat."[1482] In Morrison's experience, these patients had frequently been told that they were neurotic and had been given the diagnosis of "globus hystericus." Dysphagia caused by deformity of the esophagus by protruding spurs of cervical osteoarthritis was reported.[2004]

Pathology. Osteoarthritis of the spine was most probably caused by natural changes of age in bodily tissues; prevalence of thoracic and lumbar spondylosis in both men and women between the fourth and eighth decades was noted.[245] Common sites were the zeniths of spinal curves,[245] and insertions of particularly powerful tendons or ligaments important in maintaining the orthograde posture in man.[165]

Though vertebral osteophytes were not a part of the degenerative process in

hyaline articular cartilage of diarthrodial joints,[463] the two processes might coexist,[353] and the prognosis depended pathologically on associated vertebral changes.[166] The significance of degeneration of discs was disputed: it was considered to be an important factor,[413, 1524] or at least a predisposing or precipitating cause,[353] or not present often.[166] Senile shrinkage of the cervical intervertebral discs, rather than trauma, was possibly the cause of arthritis of Luschka's joints.[353]

Roentgen Studies. Osteophytes became visible in the fourth decade and appeared somewhat earlier in men than in women. Of 151 patients with painless backs (mostly manual workers from 18 to 82 years of age), 122 had some degenerative changes indicated in the x-rays.[183] Of 50 hospital patients more than 50 years of age, 82% had marginal osteophytes of the anterior borders of vertebral bodies, but the finding per se was not of much importance in the production of symptoms or signs.[1578] Many patients who on x-ray examination showed osteoarthritic changes in the cervical spine had no symptoms referable to this finding;[640] oblique x-rays of the cervical spine might confirm osteoarthritis of Luschka's joints, but did not indicate the severity of symptoms.[353]

The aging vertebral column in man and dog was essentially the same roentgenologically, even though canine vertebrae did not support body weight; vertebral lipping was identical on the bony margin of the vertebral body.[209]

"Physiologic ligamentous calcification" was the most plausible explanation for vertebral ligamentous calcification in 53 patients in the older age groups who revealed no other evidence of disease of the spine. [This is apparently similar to "senile ankylosing hyperostosis," reported by Forestier and Rotes-Querol (Tenth Rheumatism Review).—Ed.] Decreased mobility of the spine with aging preceded ligamentous calcification; the latter might actually result from the relative immobility.[1934]

Treatment. Reports chiefly dealt with osteoarthritis of the cervical spine. Cervical traction was combined with thermotherapy,[1181] but results of cervical traction were sometimes disappointing.[353, 1174] Gentle manipulation under anesthesia was advocated if contractures did not respond to rest and physical therapy.[1174] In severe cases, operation was needed to relieve nerve pressure.[636]

Weekly to biweekly injections of cortisone (37 patients) or hydrocortisone (nine patients) around cervical, thoracic or lumbar vertebrae or within the sacro-iliac joints produced subjective improvement in 40 patients.[397] Injection of hydrocortisone into discs produced "rapid remissions" in 37 of 55 patients (67%) with disease of intervertebral discs.[636]

Early postoperative abdominal and spinal flexion exercises were advised for patients with osteoarthritis of the spine who were operated upon for lumbar disc syndromes.[87]

Backache and Sciatica

Many writers dealt with the subject of backache, and papers concerned with the "disc problem" were especially numerous. Symptoms, physical findings, roentgenographic findings, diagnosis and differential diagnosis were reviewed.[256, 302, 445, 511, 703, 714, 776, 1008, 1209, 1580, 1772, 1804, 1849, 1850]

To simplify the problems of backache it was suggested that in practically all instances backache was caused by compression or irritation of nerve roots and

decreased excursions of the dural sac and roots. In most, the basis was an abnormal or a diseased disc. In others, abnormal anatomic structures, including spondylolisthesis, spina bifida occulta and transitional fifth lumbar vertebrae were responsible.[776] To others, the problem was more complicated; backache was attributed to: (1) organic lesions, (2) postural, occupational and mechanical stresses, and (3) psychologic factors, including psychoneurotic reactions and malingering. In many instances, elements of all three categories were present. A "thoughtful analysis" of these factors was essential to proper management of a patient with backache.[1008]

Backaches frequently subsided without therapy but sometimes left residual symptoms often attributed to psychoneurosis. These symptoms were at times regarded as incurable by both the patient and his physician.[1772]

Backache from Lumbosacral and Sacro-iliac Sprains and Strains and from Sacro-iliac Subluxations. In recent years, diagnoses of sacro-iliac and lumbosacral strain have been generally abandoned in favor of the idea that basic causes of backache are apt to be either traumatic lesions of intervertebral discs or degenerative changes of discs secondary either to aging or to repeated minor injuries.[1580] The concept of sacro-iliac and lumbosacral strain was difficult to define, and hence was often a "waste basket" diagnosis.[327] It was again suggested that man has not fully adapted himself to the upright posture.[1040] In fact, the change from quadripedal to bipedal or upright posture has not yet resulted in anatomic adaptation of the structures in the back capable of compensating for excessive stresses and strains.[1580] The term "lumbosacral backache"[258] or "lumbosacral syndrome"[1129] was preferred to the term "lumbosacral strain." [But none is a very specific diagnosis.—Ed.] In the past this condition was known by many names, including "lumbago," and pain was attributed to compression of nerve roots,[776] hyperextension of the spine,[1129] overriding of lumbosacral facets,[258] strains of ligaments and muscles or acute back strains,[256, 511] and a number of other conditions.[445, 703] The subject of sacro-iliac subluxations was ignored or considered to be nonexistent by most writers; however, one stated that sacro-iliac relaxation was in some manner responsible for osteitis condensans ilii.[728]

Diagnosis and treatment were thought to be similar for patients with backache in the lumbosacral region, whether or not a protruded disc was present.[258] Conservative treatment was generally approved. Patients were advised to avoid hyperextension of the back, to sleep on either side with the knees drawn up, to sit with the pelvis rotated forward, and to stand "correctly," with the lumbar spine "flattened." Exercises to strengthen the abdominal muscles and "posture" exercises were said to be essential to this program. Braces and casts were also approved.[258, 511, 1008, 1040, 1129, 1580, 2231] Vertical spinal traction was applied with the patient suspended by means of a padded and well fitted corset around the lower thorax and attached to an overhead cross bar with a self-locking hoist system. Countertraction was exerted through a pelvic belt attached to a cross bar firmly fixed to the floor.[714] "Hanging," a maneuver during which the patient lies prone with the lower extremities dangling over the elevated end of an examining table in such a way that the low back and hips are flexed, was also said to relieve backache.[1129] Manipulation without anesthesia resulted in improvement within one week in 50% of the cases, and within three weeks in 87%.[445] Injections of a mixture containing camphor and salicylates were also approved as a treatment for backache.[264] [Details of the composition of this mixture

were not reported. No control data were noted.—Ed.] A method of treatment was reported for "sacro-iliac relaxation" by a local injection of Sylnasol (a mild sodium salt of a fatty acid). Experimental work in rabbits showed that injection of this drug into fibrous tendons promoted the production of new connective tissue. This substance was used in the treatment of 253 patients over a 14-year period. Vertebral and pelvic joints were injected without unfavorable effects, and relief of symptoms followed in more than 80% of the patients.[860] [No details were given to characterize this ailment. No control studies were presented.—Ed.]

Industrial Backache. Although low back pain was still a major problem in industrial medicine, few papers on aspects other than intervertebral discs appeared.[999, 1045, 1795, 2239] Diagnosis as early as possible was advised. Pain was the basic factor distinguishing between mild and severe injury. The degree of limitation of motion, a measure of disability, was considered to be an expression of the pain threshold for a particular individual. In one study, mephenesin, a skeletal muscle relaxant, was used in conjunction with other measures to relieve pain and muscle spasm. Relief of pain was important in therapy, and often could be accomplished only by relieving muscle spasm. Physical measures such as diathermy, infrared heat and injections of procaine hydrochloride did not hasten recovery unless accompanied by relief from pain. Among 91 patients with low back injuries, 79 (86.8%) responded satisfactorily to this treatment. An educational campaign dealing with back injuries was described. The project was carried out in a plant which employed 17,000 workers. There was a reduction in time lost due to back injuries from 37.5% before the program to 0.1% afterwards.[1045] [A most successful program, judging from this description.—Ed.]

Among 1,163 men observed during a five-year period in Great Britain, trauma had preceded back pain in 664 (57.1%). Usually flexion and rotation of the spine were involved in the injuries. Causes of trauma were classified. Nontraumatic back pain occurring in 499 (42.9%) of these men was analyzed. The cause was often purely speculative. On arising from bed, from a chair or from a squatting position, the patient suddenly found the back painful, or a dull backache appeared for no apparent reason. Thick-set, stocky men with a flat lumbar spine constituted 85% of these cases. Slim men of average height seldom experienced nontraumatic backache. Treatment consisted of infrared therapy, massage, manipulation without either anesthesia or sedation, and short wave diathermy with strapping. The term "slipped" disc was avoided. A diagnosis of either strained back, fibrositis, lumbago or sciatica was acceptable to the patient. Therapy was empiric but effective.[2239]

Defects considered to be either of actual or of potential significance were present in 1,174 (25.4%) of 4,654 roentgen examinations of the lumbosacral spine made during preëmployment examinations. Approximately 10% were rejected for employment because of spinal defects, but those with seniority established by prior employment were accepted despite roentgenologic defects. Persons without seniority were rejected if the spinal defects fell into the following categories: (1) acquired defects, such as fractures, disc abnormalities, Pantopaque in the neural canal, and previous spinal fusions; (2) osteoarthritis of any degree; (3) defects involving the lumbosacral joint, including transitional vertebrae and spondylolisthesis; (4) abnormal curvatures of marked degree, and (5) miscellaneous defects such as tumors (hemangiomata and osteochondromas), osteochondritis and marked asymmetry of either lumbosacral joints or sacrum not falling into other classifications. Compensation claims due to back injuries were not entirely eliminated by this program but were reduced, since fewer claims based on structural defects were made.[1795]

Low back pain in industrial and forest workers in Sweden had been present at some time in 80% of the working force, but in only 15% of those 15 to 20 years of age. Symptoms usually appeared before 30 years of age. There was no relationship between backache and either static postural deformities, body type, blood pressure, physical tolerance, gastric disturbances, allergic diseases or varices. Among 77% of the patients between 35 and 49 years of age, x-ray changes indicating disc degeneration in the lumbar spine were present, and there was a definite correlation between low back pain and disc degeneration. No correlation was noted between the occurrence of backache and congenital anomalies such as spondylolysis, spondylolisthesis, or transitional and asymmetric vertebrae.[999]

Postural Backache. Backache due to postural abnormalities was again considered to originate during adolescence, though symptoms might be postponed to the fifth or sixth decades, at which time degenerative changes could complicate the picture. Faulty body mechanics were said to lead to "sway back" or increased lumbar lordosis, sagging, obese abdomen, flat chest, protruding chin and poor trunk musculature. Abnormal spinal alignment may cause unusual muscular and ligamentous pulls and strains; proper alignment and proper weight bearing reduced such strains.[1580] Fatigue tended to aggravate lordosis—thus symptoms appear late in the day, or after the patient has been standing in one position for a long time. A proper position during standing, sitting and sleeping was recommended.[799]

Postural fatigue and backache also resulted from nervous tension, which provokes the "on guard" attitude. Many persons with postural backache were reported to be unable to rest when tired, and to become "keyed up" instead of getting sleepy when fatigued.[1008] The abnormal posture of pregnancy, with exaggerated lumbar lordosis, was found to be a frequent cause of backache.[304] Fatigue accompanied by ligamentous and muscular strains was often followed by increased lumbar lordosis, a transverse position of the sacrum and an increased lumbosacral angle. After a time the increased strain on the lumbosacral articulations led to stretching of ligaments, overriding of facets and development of degenerative arthritis.[1580] [This would be regarded as secondary osteoarthritis.—Ed.]

Prevention of backache by correction of abnormal posture was considered to be essential.[799] The patient should be taught to flatten his lumbar spine against a wall.[258] Exercises to strengthen gluteal and abdominal muscles were recommended. Such a patient should sleep either on the side with the spine flexed or on the back with a pillow under his knees. When he is standing at a table or bench a foot should be rested on a low step in order to flatten the back.[1580]

Spondylolisthesis. The term "spondylolisthesis—falling of the vertebrae," was used first by Kilian in 1853 to describe extreme forward dislocation of the fifth lumbar vertebral body over the sacrum, with partial blocking of the pelvic inlet.[1653] The term has come to mean either forward or backward displacement of one or more vertebral bodies. A defect in the isthmus or pars interarticularis was usually found to be responsible, but other anomalies, including fractures and destructive lesions (inflammatory or malignant) of the isthmus or articular processes, might be the cause. Slight degrees of spondylolisthesis could result from erosion of facets caused by degenerative arthritis.[416, 1527, 1653] [Displacements without defects in the neural arch are termed "pseudospondylolisthesis."—Ed.] Differentiation of spondylolisthesis due to isthmus defects from pseudospondylolisthesis due to degeneration of facets was possible with the aid of lateral roent-

genograms. Sometimes oblique views were needed.[1653] Pseudospondylolisthesis was observed to occur most frequently at the fourth lumbar segment, but occurred also at other levels.[863] In some instances, spondylolisthesis was demonstrated in roentgenograms only if made while the patient was erect.[728] A review of 3,000 spinal roentgenograms of young men showed 21 with forward displacement of one or more vertebrae associated with degenerative arthritis. Two showed cervical displacements, whereas in 19 the lesion was located in the lumbar region.[1653]

Low back pain and stiffness, either with or without sciatica, were usual symptoms of spondylolisthesis.[416] Diminished or absent reflexes were sometimes noted, and muscle atrophy due to damaged spinal nerve roots[2255] or other evidence of radicular irritation was encountered in two thirds of the cases.[776] Distribution of pain was said to mimic that of the "compressive" type of sciatica.[10] Coexistence of a neoplasm of the cauda equina and spondylolisthesis was observed in one patient.[1085] Among 46 cases of spondylolisthesis, two had associated tuberculosis of the spine. Another showed a lesion of the cauda equina resulting in bladder dysfunction and saddle anesthesia.[10] In one patient complete destruction of the cauda equina was observed.[1527] A case report described a patient in whom assisted vaginal delivery was possible in the presence of spondylolisthesis.[272]

Pain of spondylolisthesis was attributed to abnormal pressures on damaged and arthritic joints,[1580] impingement of malaligned bony elements, abnormal stresses on fibrous and ligamentous structures, and prolapse of intervertebral discs.[237, 1447, 1527, 1580] A tumor-like mass of callus at the pseudoarthrosis located at the isthmus defect[10, 776] and compressions of nerve roots by a movable fifth lumbar lamina were also suspected.[10, 776, 2255] Others considered disc degeneration with protrusion of nucleus pulposus to be rare,[10, 416, 776, 2255] and some were not impressed by the occurrence of callus at the site of isthmus defects.[237] Increased lumbosacral angle and arthritic changes present in some patients with severe disability were other possible sources of pain.[416] Among 137 residents of an old people's home were 12 with anterior spondylolisthesis at either the fourth or the fifth lumbar segment. No history of injury was elicited, and no disability resulted.[764]

The etiology of isthmus defects associated with spondylolisthesis was not settled. A majority of opinions favored a congenital origin;[728, 776, 863, 2255] however, trauma was sometimes thought to be a factor,[272, 416, 728] or the only factor.[1527] Isthmus defects were suggested as being identical with stress or fatigue fractures, such as the "march fracture." The pars interarticularis is the most slender part of the arch, and is therefore especially susceptible to shearing stresses. Bony union did not occur in all instances, and fibrous union with callus-like bony masses may project into the spinal canal.[861, 862] These bony masses were seen projecting posteriorly on oblique views of the spine.[863] The occurrence of spondylolisthesis in identical twins was reported. Symptoms occurred following trauma in one sister at the age of 36 and in the other at the age of 38. This was considered to be further proof of the congenital origin of this condition. Prespondylolisthetic vertebrae may not be displaced until stresses of adult life, marked trauma or occupational accidents are experienced.[2100]

A majority of the patients were relieved without surgical procedures. Among 201 patients in one series, only 29 needed surgical therapy.[416] Those without compression of nerve roots can in many instances be treated successfully by correction of posture, back exercises, lumbosacral supports, a firm mattress, heat, massage and limitation of activity.[416, 1580] Removal of protruded discs followed by spinal fusion was necessary in some.[340] Removal of lumbar lamina and either the spine or arch of the displaced segment, together with decompression of the fifth lumbar and first sacral nerve roots, was recommended.[237, 2255] Spinal fusion was done in selected

cases [2255] or in all.[237] Others recommended removal of a loose lamina and dissection from the nerve roots of a fibrocartilaginous mass at the site of the isthmus defect without doing a spinal fusion.[776]

Reverse Spondylolisthesis. Reverse spondylolisthesis followed degeneration of intervertebral discs with narrowed interspaces and stretching of structures supporting the apophyseal joints. Instability of these joints led to posterior subluxation and posterior displacement of vertebral bodies cephalad to the degenerated disc.[764, 863, 1331] Fixation of the spine in forced extension, such as occurs during bending forward and lifting, carrying a weight above the level of the waist, standing up from a sitting position or lying on the abdomen, may be accompanied by powerful contractions of sacrospinalis muscles which acted like a bow-string and tended to cause posterior subluxation of apophyseal joints, or reverse spondylolisthesis. Thus pain in the lumbosacral region, buttocks and thigh may result. Roentgenograms failed to show reverse spondylolisthesis unless the patient was standing.[1331]

This condition was a frequent finding at the postmortem examination in spines showing degenerative changes in intervertebral discs.[1331] Among 137 residents of an old people's home, roentgenograms showed nine with reverse spondylolisthesis. In two the lesion was in the dorsal region and in seven in the lumbar spine. All showed degeneration of adjacent discs. There was no history of trauma, and the condition was not disabling.[764] Posture training and exercises to strengthen abdominal and gluteal muscles were used to decrease the lumbar curve; some patients needed spinal support.[1331]

Primary Sciatic Neuritis. No new information appeared. The usual findings included tenderness of muscles, infrequent loss of reflexes, absence of paralysis, unilateral involvement, absence of cerebrospinal fluid abnormalities and normal myelograms.[495]

Osteoporosis. Some patients with osteoporosis were free of symptoms; others were disabled by severe pain. Onset of pain was gradual or sudden; the duration of symptoms ranged from a few days to many months. In some pain was intermittent. The character varied from dull backache to severe, sharp, localized pain which radiated to buttocks or legs. Movements, jarring and flexion of the spine aggravated pain. Coughing and sneezing often increased the pain and suggested the presence of pressure on roots of spinal nerves.[427, 1022, 1469] The degree of disability could not be correlated with severity or extent of radiographic findings. Thus, some with severe pain showed only minor changes in x-rays;[1469] others with extensive deformities had no pain.[183, 1469] It was suggested that symptoms were caused by compression fractures of vertebral bodies.[1825] In spite of severe deformities, compression of the spinal cord was not generally present.[427]

Decreased density of vertebrae, pelvis, ribs, sternum and femur was often present. Long bones and the skull were apt to be involved later and to a lesser degree than was the spine.[1022, 1469] Increased translucency of bone with a ground glass appearance and poor definition of trabeculae was an early finding. Later, blurring disappeared, trabeculae were well defined and their meshwork became wider than normal. Individual lamellae were thinner.[1190] In extreme cases the trabecular structure was almost invisible and the cortex narrowed so that contrast between bone and soft tissues was slight.[427] Pseudofracture lines were characteristic of osteomalacia or

Milkman's syndrome.[427, 1022, 1190, 1469] From 30 to 60% of calcium was lost from bone before osteoporosis could be detected by roentgenography.[427, 1190, 1469, 1971]

Osteoporosis was again attributed to decreased activity of osteoblasts, with inadequate production of organic matrix or osteoid. The genetic, nutritional, endocrine and mechanical factors which influence growth and maintenance of normal bone were reviewed. The absence of any one or a combination of several of these factors contributed to the development of osteoporosis.[427, 704, 1469]

Senile osteoporosis was said to be a universal feature of aging bones[1469] and identical with postmenopausal osteoporosis.[427, 1022] Decreased physical stresses and nutritional and vitamin deficiencies were described as additional factors responsible for senile osteoporosis.[427, 1469] A study of 94 women with artificial menopause induced by either surgery or radiation indicated that osteoporosis was not precipitated by these procedures. Among 28 women showing osteoporosis and in whom menopause had been induced, no evidence was found to indicate that osteoporosis occurred at an earlier age because of the artificial menopause.[532] [The cause of idiopathic osteoporosis remains unknown. No new hypotheses were suggested.—Ed.]

The term "post-pregnancy osteoporosis" was suggested for the syndrome consisting of backache and compression fractures of osteoporotic vertebrae appearing during pregnancy. This condition was not thought to be the same as osteomalacia. A high level of plasma-corticosteroids resulting from the pregnancy was suspected as a possible cause.[1536] Prolonged administration of either adrenal steroids or corticotropin was followed by multiple fractures appearing in persons already predisposed to osteoporosis by chronic rheumatoid arthritis,[472] and in some not so predisposed.[1022] Compression fractures occurred spontaneously in some, and followed the application of little force other than the bearing of the weight of the upper part of the patient's body.[427] A calcium tolerance test considered to be adequate to uncover asymptomatic early cases of osteoporosis was reported.[1971] Among female patients the chances for osteoporosis were six times greater than among male patients. A loss of height was stated to increase the odds in favor of this diagnosis.[427] Osteomalacia resulting from resistance to vitamin D, accompanied by low serum phosphorus, increased alkaline phosphatase, and pseudofracture lines, needed to be differentiated from osteoporosis.[618] Multiple myeloma, hyperparathyroidism, Paget's disease, Cushing's syndrome, acromegaly and hyperthyroidism were also responsible for osteoporosis.[427]

A high protein diet, an adequate amount of vitamin C and D and a calcium intake of 800 to 1,000 mg. were recommended for treatment of osteoporosis. Strontium may be absorbed and retained independently of calcium. However, no proof was forthcoming that strontium induces additional formation of matrix.[1325, 1469] Androgens and estrogens were recommended as effective therapy for osteoporosis.[204, 427, 1325, 1469] An androgen with strong anabolic properties and only slight masculinizing effects, methyl androstenediol, was also reported to be of value.[95, 427] Except in one case,[1325] no increase in bone density was observed after hormone therapy.[95] Pain was relieved in from two weeks to two months, but an improved roentgen appearance was not noted until two years.[427] Rapid mobilization of patients with compression fractures was advised. Prolonged bed-rest and immobilization were considered to be contraindicated. For patients unable to be ambulatory, vibrating mattresses and oscillating beds provided stresses needed to prevent further decrease in osteo-

blastic activity. [This needs to be confirmed.—Ed.] Light spinal supports and physical therapy, which included postural and muscle strengthening exercises, were said to be of value.[1469]

Hypertrophy of the ligamentum flavum was one of a group of miscellaneous lesions discovered at the time of operation in patients with "lumbo-sciatica of distal origin."[1345] [This condition is not believed to be of clinical significance. —Ed.]

Malignant Disease of the Spine. Many writers stated that patients with severe, persistent backache who are not relieved by usual measures should be suspected of having a malignancy. [This point is worthy of strong emphasis.—Ed.] Metastases to bone may be expected in as many as 40% of patients dying with carcinoma.[195, 302, 703, 1192, 1549] Among 1,200 persons undergoing surgery for intervertebral disc lesions, 19 were found to have malignant neoplasms. Twelve had metastatic carcinoma and seven had primary tumors. In 11 patients proved to have malignancies, nothing abnormal was noted in roentgenograms of the spine.[1549] In carcinoma of the prostate, kidney, thyroid and lung the primary lesion may be silent. Collapse of a vertebral body infiltrated with neoplasm caused compression myelopathy.[139] An intervertebral disc, rather than the vertebrae, was invaded by metastatic carcinoma.[1192]

Backache and radicular pains were the most frequent complaints of patients with intraspinal tumors. These symptoms occurred in 80% of the cases, and in 60% were the presenting symptoms. The condition was often mistaken for "rheumatism," prolapsed intervertebral discs, neuroses, disseminated sclerosis and various diseases of thoracic or of abdominal viscera. Only lumbar puncture excluded a tumor as the cause of persistent backache or root pain when no apparent cause was found with other clinical tests.[195] However, neither a manometric block nor an increased level of protein could be found in every instance.[247] An ependymoma arising in the region of the cauda equina recurred locally and extended to vertebrae, spinal musculature, pelvis, common iliac veins and inferior vena cava. This was the first report of a metastasizing tumor of the spinal cord and also the first case reported of a metastasizing ependymoma arising in the central nervous system.[2193] Pain and paresthesias located in the lower extremities, typical of polyneuritis and radiculitis, occurred in a patient with multiple myeloma. Contrary to the usual findings, there was no involvement of nerves or bone.[645] The procedure of aspiration biopsy of the spine, performed under anesthesia and with roentgenographic control, resulted in the establishment of a definite diagnosis in 20 out of 34 cases. In 11 a tumor was present, including myosarcomas, Ewing's tumors, chordomas, metastatic carcinomas, solitary myelomas, multiple myelomas and angio-endotheliomas.[709]

Gynecologic Lesions. Almost every disease of the uterus and adnexae was blamed for backache.[703] Malignancies of the uterus and ovary as well as inflammatory disease of adnexae were reported as causes of backache.[1915] Pelvic ligamentous relaxation occurs during pregnancy and during menstruation, but the importance of this condition as a cause of backache was difficult to evaluate.[2213] [We agree.—Ed.] In the pregnant woman, postural backache may result from lordosis (the "pride of pregnancy" position) necessary to maintain the center of gravity for bipedal locomotion. Flexion or flattening of the low back, by lying on the back with the hips and knees flexed at right angles, usually gave rapid relief from pain. Such improvement in symptoms was not the rule in vertebral, cord or visceral disease.[304]

Gastrointestinal Lesions. Visceral diseases, including peptic ulcer, and carcinoma of the pancreas, liver, stomach, colon and rectum, were included among the causes of backache. Such pain was especially severe if peritoneal tissues were involved. Backache of visceral origin did not conform to usual patterns of musculoskeletal disorders, and was not relieved either by lying down or by flexing the spine, as in patients with postural backache. Neither bending, coughing nor sneezing aggravated this pain, and it was not reproduced by active and passive movements of the spine. Retroperitoneal lesions were suspected if: (1) the patient experienced episodes of backache located anywhere from the upper thoracic to the sacral region, either with or without radiation; (2) pain appeared without apparent cause, and when the patient was at rest, and (3) pain lasted for a few hours and then disappeared spontaneously.[302, 703]

Spinal Osteochondritis (Adolescent Kyphosis); Juvenile Epiphysitis; Scheuermann's Disease. This condition was again observed to affect most frequently those between the ages of 12 and 17, and often to cause pain located in the mid-dorsal region. This condition was attributed to prolapse of an intervertebral disc through a weakened zone in the anterior portion of the end plate, at the site of a previous penetration of an obliterated blood vessel. This was thought to interfere with growth of adjacent vertebral bodies. As a result, affected vertebrae became wedgelike or elongated. Resulting kyphosis led to still other changes in the spine.[183]

Spinal deformities associated with spinal osteochondritis included posteroanterior wedging of vertebral bodies, irregularity of upper and lower margins of vertebral bodies, either with or without indentations caused by Schmorl's nodes, narrowing of intervertebral spaces, anterior marginal osteophytosis and spondylarthrosis (hypertrophic arthritis) of apophyseal joints.[2226] Among 151 persons employed at heavy work, 15 showed spinal osteochondritis. None of the 15 gave a history of backache. Those affected ranged in age from the early twenties to over 70. Even though the condition appeared during youth, some affected persons remained free of symptoms even into old age.[183]

Among 365 forest workers, apprentices and industrial workers, the incidence of kyphosis was 14%. About three fourths of these were associated with wedging of vertebral bodies and characteristic changes in epiphyseal plates. Both the kyphosis and the Scheuermann changes occurred twice as often among forestry workers and their apprentices as among industrial workers. Although heavy work may have been a factor in causing these lesions, the early age at which this occupation was started (usually at 12 to 13 years, and before ossification of vertebrae was completed) was probably more important.[999] A further study by the same investigator disclosed kyphosis among 13% (146) of 1,200 workers in various occupations. In a majority this kyphosis was of the Scheuermann type. The incidence was about the same in persons doing heavy and light work. Backache was not more frequent among kyphotic persons than among the others. Mild episodes of fatigue and pain in the dorsal region occurred in 10 of the 146 patients with kyphosis. Three experienced pain accompanied by radiation resembling intercostal neuralgia. This symptom occurred somewhat more frequently among persons with kyphosis than in others.[998] Differentiation of this condition from tuberculosis of the spine, which it resembles both clinically and radiologically, was emphasized.[1203] Open anterior vascular grooves, the site of the intersegmental artery in the cartilaginous anlage of the vertebrae, were observed among children aged six to 10 years with a dorsal round back posture. Persistence of these grooves was believed to be the predisposing

factor in the wedging of the vertebrae. Measures to aid in relieving stresses on the dorsal spine were recommended to aid in minimizing this deformity.[671] Spinal cord compression caused by herniation of a thoracic disc occurred in a boy aged 17 with juvenile kyphosis. Symptoms and findings were relieved by surgery.[2180]

Diseased Facets. Acute episodes of backache characteristic of "lumbosacral backache," and caused by damaged apophyseal joints, were often confused with the intervertebral disc syndrome. Following disc degeneration the apophyseal joints of lumbar vertebrae were sometimes found to override and thus to cause narrowing of the intervertebral foramen. This condition resulted in pressure on the nerve roots, with sciatica and backache. In addition, abnormal mobility associated with this disorder may lead to the development of degenerative arthritis at apophyseal joints. Conservative treatment aimed at keeping the low back flat, or even reversing the lumbar curve, was recommended.[258, 618]

Backache due to a "loose facet" was said to be episodic and characterized by sudden onset of excruciating discomfort, followed by rapid relief of symptoms. The patient feels something "lock" at the onset and feels something "move" at the time he obtains relief. Physical examination may show only severe paravertebral muscle spasms. Surgical exploration has shown articulating facets attached to laminae by fibrous tissues. In some instances this condition may be developmental. In others, fractures following surgery for protruded intervertebral discs were the cause. Apparently attachment of facets to laminae was weakened by removal of bone at the time of operation. Roentgenographic examination has been of little aid and has not been diagnostic in these instances of "loose facet." Strains, sprains, hysteria and malingering were suspected prior to surgical exploration. Neither prolonged immobilization nor a support was of any benefit, as symptoms invariably recurred when these measures were discontinued.[1138, 1139] A whip-lash injury of a lumbar neural arch associated with fracture of spinous processes and of an inferior facet was described.[1450]

Osteoarthritis of the apophyseal joints at the level of exit of the first lumbar nerve roots was suggested as the cause of a newly recognized yet reputedly common musculoskeletal syndrome[1241] called the "first lumbar root syndrome." This painful condition was associated with tenderness and muscle spasm occurring over part or the whole of the first lumbar segments, unilaterally or bilaterally. [This condition is worthy of further study.—Ed.]

Congenital Anomalies. Spondylolysis, spondylolisthesis, spina bifida, sacralization of the last lumbar vertebra, lumbarization of the first sacral segment, asymmetric apophyseal joints, increased lumbosacral angle and other anomalies were believed to predispose to instability of the back and to cause backache.[340, 728, 1209, 1580, 1850, 2014] Symptoms and findings related to these ailments were found to be nonspecific, hence the diagnosis was dependent entirely upon findings in the roentgenograms.[1580] Conservative treatment was recommended for all. Spinal fusion was approved only in the event that relief was not obtained with simpler measures.[340]

In patients with spina bifida occulta, anlage of the spinous process belonging to the first sacral segment was held on a diaphragm of ligamentum flavum and in this location exerted pressure against either the dural sac or the first or second sacral nerves when the back moved. The clinical picture simulated a herniated intervertebral disc, differing only in that tenderness was noted by the patient when pressure was exerted over the loose spinous process.[776]

Defects of the fifth lumbar neural arch, sometimes considered to be developmental in origin, may possibly have resulted from spontaneous fractures or so-called "fatigue fractures."[862] Callus-like masses of bone projected into the spinal canal opposite such defects and may have been responsible for backache.[861] Other congenital

anomalies responsible for backache included narrow lumbar spinal canal,[2139] and cysts of meningeal origin located in the lumbar and sacral regions.[1888, 2035]

Psychogenic Backache. "Functional" or psychogenic backache needed to be considered in the differential diagnosis of every backache,[327, 1008, 1250, 1580, 1850, 2037] but diagnosis by exclusion was inadvisable.[1250, 1850] In some ways the malingerer as well as the patient who exaggerates his symptoms presented findings similar to those of the patient with psychogenic backache. The pain was described as "severe all the time," "never any better," "hurts everywhere," "nothing helps," etc. It was not consistently affected by the weather, and was never relieved by medication or treatment of any type. On examination the patient resisted movements and had a "touch-me-not" attitude, and the physical findings were inconsistent.[1008] These patients assumed unusual postures, often of a grotesque nature, localized pain poorly and described it vaguely. Conflicting, distorted, paradoxic and extreme reactions to examinations and treatments were seen both in patients with psychogenic backache and in those suspected of malingering.[1580] In addition to pain, these individuals often complained of pulling, throbbing, tightness and pressure sensations. Areas of extreme tenderness were often present. Vasomotor instability and hyperhidrosis were commonly found.[2037] Muscle weakness of the "jack-knife" variety (early, sustained muscle strength followed by a sudden giving way), not characteristic of weakness due to paresis, was often present.[274] Headaches, muscle cramps, involuntary muscular movements, difficulty in breathing and easy fatigability were also characteristic complaints in persons with this condition. This was termed "muscular reactors' syndrome," because the patient often appears to be tense, assumes a rigid posture, has shallow diaphragmatic breathing and sweats excessively. Backache was only one part of the psychoneurosis, and was not necessarily the presenting complaint.[1250]

The neuroses, including hysteria, were difficult to differentiate from malingering, and the latter was most difficult to prove, inasmuch as there were no specific tests or methods to rule out "backache" with certainty.[1580] The tendency to disbelieve such patients and to brand them as psychoneurotic on the basis of slight inconsistencies was deplored.[1121] [Overemphasis on functional aspects of backache may be deplorable. However, this problem will not be solved by denying the existence of hysteric phenomena. A more general discussion of this subject is included in the section on Psychogenic Rheumatism.—Ed.]

Criteria for detecting complicating psychologic factors were derived from a study of 36 patients with low back pain. These criteria concerned the patient's attitude toward symptoms and treatment, also the reaction to pain and illness. The following characteristics were designated criteria of functional backache: a vague history, unreliable as to chronology and containing numerous irrelevant details; expression of open or veiled resentment toward and criticism of doctors and ancillary personnel because of alleged mismanagement; detailed descriptions of symptoms and reactions to them; difficulties in localization and description of pain and other symptoms; failure of usual modes of therapy to give relief from pain; and accompanying neurotic symptoms. Nearly 50% of patients with backache showed signs or objective findings of organic lesions also. A patient's illness should not be considered in terms simply of psychiatric or orthopedic disease. Both may be responsible for symptoms in many instances.[274]

Osteitis Condensans Ilii. Osteitis condensans ilii, primarily a roentgenologic diagnosis, was based upon the findings of sclerosis in only the iliac side of the sacro-iliac joint. This condition may be either unilateral or bilateral and usually involves the lower two thirds of the iliac margin. The joint was perfectly free. The clinical importance of this condition was in doubt. Some patients with this finding had persistent back pain, while others did not.[1856, 2174] A relationship to pregnancy was said to be coincidental. In one group, eight of 20 patients were males. The course was generally benign. Treatment was either conservative or deferred, since nearly all became asymptomatic within a short period of time.[1856] [See also osteitis condensans ilii in section on Rheumatoid Spondylitis.—Ed.]

Herniation of Fascial Fat and Episacroiliac Lipomas. Panniculer lumbosacral hernias and episacral lipomas were again discussed as causes of backache. Onset of symptoms was said to be insidious. Pain was sometimes severe. A tender nodular mass over the sacro-iliac region, together with radiation of pain into the leg, was characteristic. Local injections with procaine solution gave temporary relief, and repeated injections sometimes gave permanent relief. Surgical excision may be necessary.[674, 1850] [The wave of enthusiasm for this entity as a bona fide cause of backache seems to be subsiding.—Ed.]

Rupture of lumbodorsal fascia with subsequent fibrosis of subfascial fatty tissue, which becomes adherent to fascia at the site of injury, was also designated a common cause of backache. Both the midsacral and paraspinal regions and the lateral portion of the sacrospinalis muscle in the lumbar region were frequent sites of this condition. Among 109 persons with backache, symptoms were attributed to this condition in 92 (84.4%). [These figures appear to us to be too high.—Ed.] Injections of procaine into the tissues gave relief in many. Surgical correction was necessary in some.[523, 524] Bilateral tears of lumbosacral fascia or aponeuroses with protrusion of retroperitoneal fat through the defects were said to be responsible for backache.[1258] The "multifidus triangle syndrome," attributable to injuries of either ligaments or fasciae, was described. Local injection of a mixture of hydrocortisone, hyaluronidase and procaine hydrochloride resulted in recovery within four weeks. Some were relieved after only one injection.[119] [No controls. It is difficult to evaluate this report.—Ed.]

Cramplike pain and aching in the region of the lower back, hip and thigh, initiated by activity and relieved by rest, were considered to be an intermittent claudication caused by interference with normal arterial circulation to affected muscles. The responsible occlusive vascular process involved either the aorta or the iliac vessels. As a rule, nutrition of the lower extremities was still good in affected patients.[1624] Tuberculosis of the spine as an occasional cause of backache and the disc syndrome was described in several case reports.[157, 1510]

Backache and Sciatica from Diseased Intervertebral Discs

One of the most common causes of low back pain and sciatica was again reported to be intervertebral disc protrusion, with and without associated degenerative arthritis.[249, 359, 392, 722, 776, 899, 998, 1084, 1503, 1580]

The importance of early recognition of protruded discs was emphasized. These patients should not be considered to be the exclusive province of either orthopedists or neurosurgeons.[1084] One writer pleading for conservative management stated, "I still believe we shall get the best results when we realize that

the discs belong to the patient." [249] The number of papers dealing with lumbar disc protrusion has decreased in the last few years, while the number dealing with cervical discs has increased.

Anatomy and Physiology. Numerous papers reviewed the anatomy and function of intervertebral discs.[359, 453, 722, 776, 899, 969, 970, 1517, 1772, 1774, 1908] There was general agreement among these observers. The disc was described as composed of cartilaginous end plates, an annulus fibrosus and a nucleus pulposus. End plates were growth zones of immature vertebral bodies, and during the early years of life were penetrated by blood vessels. The sites of these obliterated vessels remain as weak, striated scars into which microscopic amounts of nuclear material may herniate. In later life, granulation tissue and small vessels may grow through these defects into the discs. Large amounts of nuclear material may penetrate cartilage plates into adjacent vertebral bodies to form "Schmorl's nodes." The annulus and the nucleus are not sharply separated. Concentric layers of connective tissue or collagen fibers run obliquely between adjacent vertebral bodies making up the annulus. The intact annulus resisted displacement of the nucleus and limited expansion of discs subjected to pressure. Flexion movements of the spine resulted in opposite displacement of the nucleus. Stability of the disc depended upon its integrity. Loss of nuclear material may result in excessive movement, with damage to the annulus, apophyseal joints and posterior ligaments.[699, 1774] Discs were described as hydraulic cushions, serving as shock absorbers. The nucleus was under constant pressure, as shown by the way it bulged when the disc was sectioned.[1908]

Aging started early in discs, and these reached a peak of hydrodynamic efficiency at about 20 years of age. Late in the third decade and throughout the fourth, efficiency diminished because of enlarging defects in end plates, changes in nuclear material and degeneration of the annulus. The nucleus and annulus could be differentiated with difficulty or not at all after the sixth decade.[1774] Changes in aging human discs were studied by x-ray, crystallography and fluid absorption capacities. With advancing age the collagen of the nucleus became better oriented and degenerative changes proceeded until, in advanced ages, a stage of crystallization and fibrillation was reached. This process was associated with reduction in mucopolysaccharide content of the nucleus and loss of gel structure. In specimens from subjects more than 70 years of age, x-ray diffraction patterns indicated the presence of B-protein. This was attributed to denaturation of folded soluble protein molecules with a change to the fully extended form. A disoriented, "tightly hydrogen-bonded, B-crystalline lattice" resulted. Elasticity in the nucleus was inhibited as a result of this change. Addition of hyaluronidase to water or saline solution in which a nucleus was immersed increased the amount of absorbed fluid by 20%. No definite relationship between fluid absorption and age was detected. Varying absorption was observed in discs from subjects of the same age. A high pressure develops within intact discs on immersion in water or saline solution. Nuclear herniation was produced in one specimen, and fracture of an end-plate together with formation of a Schmorl's node occurred in another. Depolymerization of polysaccharide-collagen complexes was believed to be the cause of these degenerative changes.[1517, 1518]

The reaction of intervertebral discs to compression forces was studied by the so-called strain-gauge principle. Intact discs with adjacent vertebral bodies were removed at autopsies and placed in a special apparatus. The greater the compression of the disc, the less trauma was needed to produce a lesion.[722, 969, 970]

Pathology and Pathogenesis. A number of papers dealt with the pathology of disc degeneration.[359, 722, 776, 899, 1503, 1774, 1908] The line between normal degeneration and pathologic changes was often a fine one. Major pathologic changes included (a) prolapse of nuclear material through the annulus; (b) severe degeneration of discs, with narrowing of disc spaces and alteration in intervertebral articular mechanics, and (c) flattening with peripheral projection of homogenous discs in the aged, especially in the cervical segment. Secondary effects were considered to be especially important in cervical discs, where compression of nerve roots, arthritic changes in unico-vertebral articulations, compressions of anterior portions of the cord and vascular changes may occur.[1774]

Posterior and posterolateral defects of the annulus may be associated with extrusion of inspissated or degenerated nuclear material with flexion and extension of the spine. Often a concomitant injury to cartilage plates occurred with hemorrhage from the spongiosa of vertebral bodies. Amorphous or granular deposits of calcium were observed in both the nucleus and the annulus of prematurely aged discs.[899] Discs were said to not "slip"—rather, swelling to an abnormal volume with bulging to form a protrusion. A sequestrum of degenerated nucleus may be extruded and press on nerve roots, with resulting sciatica.[359]

Osteophyte formation was said to be a manifestation of disc degeneration. Narrowing of interspaces with loss of support and resultant instability may cause posterior or apophyseal joint damage. Fractures of articular facets may result from trivial injuries. Overriding and subluxation of articular facets were occasional results of this process.[249, 899, 1774]

Relationship to Trauma. Disc protrusion occurred if a patient lifted or strained while the back was flexed, or if he sustained some other type of injury.[249, 1084, 1503, 1869] In 25% of the cases no history of trauma was obtained.[1580]

Repeated trauma or a single trauma was believed to be the usual precipitating factor in younger individuals. Nevertheless, in nearly all of a series of teen-agers with disc lesions, trauma had been slight or absent. Only rarely did onset of symptoms follow athletic participation. Nuclear material removed at operation from patients of this age group resembled that found in adults with similar lesions, and clinical findings were also similar to those encountered in older individuals.[1213]

Protrusions of cervical discs with spinal cord injuries were reported to fall into two groups. In the first were those following an injury to the head or cervical spine, with severe and perhaps total transverse lesion of the cord. In the second were those with damage of the cord, without known injury to the head. Cord compression in both the cervical and dorsal regions resulted either from disc protrusions of sudden onset or from slowly developing protrusions.[1547]

Congenital anomalies, such as sacralization [39] and spondylolisthesis,[10] predisposed the individual to disc lesions. One writer stated that deficiency of vitamin C played a role in their development.[1394] Experimental animals (voles), under the stress of daily fighting, showed a significant increase in size of nucleus, proportional to increased size of adrenals, thymus and spleen. Increased activity of the adrenal cortex was believed to be responsible. This writer suggested that increased size of the nucleus pulposus, together with increased pressure within the disc resulting from disturbed fluid balance, might be factors contributing to disc degeneration in humans.[1847] [It appears unlikely that this report adds anything of value to a solution of the problem of degeneration of discs.—Ed.]

Calcification of Intervertebral Discs. Calcification of discs in children was in-

terpreted as different from that in adults, and the two should probably be looked upon as separate entities. Calcification of discs in children was rare, and usually occurred in the cervical and dorsal spine.[2158] When present, the child may experience severe though often transitory pain. Deformity and limited movements may result. The calcific deposits were located in the nuclei. The process was reversible. Calcification may follow trauma and may result from calcification of a hematoma.[2158] Among adults, calcified discs were more frequent. Symptoms were generally absent. Usual sites in adults were the lumbar and lower dorsal segments. The calcium was generally situated at the periphery of the disc, in the annulus. Chronic wear and tear was believed to be responsible in adults.[1834] Seven new cases were reported.[1908] [Calcification of discs frequently occurs in ochronosis.—Ed.]

Cervical Discs. Several publications dealt with cervical discs.[1358, 1359, 1862] Anatomic details of bones, joints and nerves in the cervical region were reviewed at length.[1016, 1524]

Syndromes of disc protrusion in the cervical region, described by Stookey in 1928, constituted the basic clinical patterns of this condition. These syndromes varied with the site and degree of protrusion, and included (1) unilateral root compressions caused by lateral herniations, (2) unilateral root compression with both upper and lower motor-neuron disturbances on the side of the compression and with sensory findings on the opposite side, and (3) bilateral ventral pressure, with symptoms and signs referable to dysfunction of anterior columns.[1323] Distinctive features of acute and chronic types of midline protrusions were described.[2278]

In considering the pathogenesis of cervical disc disease and cervical spondylosis, Brain noted two types, etiologically distinct though sometimes clinically indistinguishable in their later stages: (1) nuclear herniation, and (2) annular protrusion. Nuclear herniation was said to occur through a defect in the annulus. Annular protrusion, observed in older individuals, was attributed to dehydration and degeneration of discs, with resulting loss of elasticity, flattening and circumferential bulging. Bodies of adjacent vertebrae showed cartilaginous and bony lipping. Osteophytes became fused and projected into the spinal canal, compressing the cord. This condition was termed "cervical spondylosis," and was distinguished from usual disc protrusions.[251, 252] The term "spondylochondrosis" was thought to be more descriptive of this condition, inasmuch as cartilaginous protrusions as well as osteophytic overgrowths were included.[58] When senile degeneration of discs and bones was present the condition was termed "primary" spondylosis. When associated with either acute trauma or congenital anomalies of the cervical spine, the term "secondary" spondylosis was preferred.[378] The respective roles of cord compression and ischemia in the development of myelopathy were not determined.[1540]

Approximately 10% of disc protrusions were found in the cervical region. Generally, lower cervical discs were involved. A syndrome consisting of pain in the cervical region about the scapula and shoulder, and often with radiation into the arm, forearm and hand, was described in numerous papers.[251, 252, 380, 448, 700, 1016, 1084, 1155, 1277, 1417, 1524, 1690, 1700, 1774, 1869, 2264]

Midline (unilateral or bilateral) protrusions with cord compression were reported to result from injuries to the head or neck. Older patients showed bulging of discs or fusion of osteophytes without having sustained any injury. The character of the resulting sensory and motor changes depended upon the size and location of either

the extruding disc or the osteophytes. Brown-Séquard's syndromes, pyramidal tract disturbances associated with spasticity and hyperreflexia as well as disturbances of equilibrium, may be present and may lead to erroneous diagnoses. A number of publications described sensory and motor disturbances associated with these lesions.[251, 252, 378, 700, 1084, 1323, 1483, 1524, 1540, 1547, 1578, 1700, 1869, 2007, 2068, 2278] When the spinal cord and nerve roots were involved, neurologic signs were at times observed before other symptoms appeared.[1578] Sensory patterns were misleading in regard to both the site and the nature of the defect. Cervical spondylosis frequently masqueraded as some other irremediable disease of the central nervous system.[2007] Whiplash injuries incurred in automobile accidents occasionally were followed by symptoms of protruding cervical discs.[380]

Among 100 patients with pain in the cervical region, either degenerative joint disease or damaged intervertebral discs were observed in 29. Some evidence of an organic disease, together with neurotic or functional symptoms, was present in 22, and functional symptoms alone were found in 49. Most persons with long-standing pain showed no evidence of an organic disease to account for the symptoms. Prognosis was poor in such individuals.[917] Both headaches and atypical facial neuralgias may accompany a protruding cervical disc, and similar symptoms were encountered with other painful lesions of the cervical spine.[1075] [It is difficult to evaluate the results of this study. The concepts propounded appear to be speculative rather than factual.—Ed.] Root pain from cervical osteoarthritis simulating angina pectoris in a 71 year old man was relieved by halter traction.[488] Acute substernal pain in six patients was erroneously attributed to myocardial infarction, but after exhaustive study no evidence of cardiovascular disease was found, and cervical osteochondrosis appeared to be the sole cause of the acute substernal pain.[1209]

A condition designated as "syndrome of Barre-Lieou" was attributed to involvement of cervical sympathetic nerves, notably the vertebral nerve and also the sympathetic network surrounding vertebral arteries. This condition was said to be associated with degeneration of cervical discs. Symptoms included atypical headaches and pain in the occipital and nuchal regions, and also pain in other regions of the head and neck. Symptoms were said to be continuous. Severe paroxysms described as throbbing, burning, stinging or pricking may be observed. Vertigo, tinnitus, pharyngeal paresthesias and vasomotor disturbances may also accompany the headache.[751, 1524]

An investigation of 1,200 male workers ranging in age from 25 to 59 years showed that heavy physical work was not an important cause of either stiff neck or brachialgia. Roentgenographic evidence of disc degeneration in this series was correlated directly with age. Among those aged 25 to 29 years, 5% showed roentgen evidence of disc lesions, whereas in those age 55 to 59 years the incidence was 90%. Those doing heavy work developed these changes at an earlier age than did those doing light work.[998] Among industrial and forest workers ranging in age up to 49 years, stiff neck and brachialgia affected a very high proportion. This condition was seldom incapacitating. Degenerative changes in discs of the cervical region were generally present. Similar changes were sometimes present in asymptomatic workers.[999] In a radiologic study of 320 persons, degenerative lesions of the cervical spine occurred as often in persons with as in those without symptoms (73 and 75%, respectively).

Thoracic Discs. Disc protrusions in the thoracic region were less common than in the cervical or lumbar areas. Men were affected more often than women (five males to three females). Neither trauma, occupation, body habitus nor heredity had any etiologic significance.[642] No large series has been reported; three publications each reported five instances[989, 1547, 1869] and one reported four.[642] Several reports of single cases were published.[2047, 2130, 2158, 2229]

Disc protrusions in the thoracic region might be either central or paracentral. Compression of the cord was occasionally noted, as were interference with long tracts and compression of nerve roots. Symptoms depended upon the site of the lesion. Myelography was of value in establishing the nature and location of these lesions.[989, 1869]

A 17 year old boy with evidence of Scheuermann's disease had disc protrusions with cord compression at the seventh, eighth and ninth thoracic interspaces. Surgical removal resulted in recovery.[2130] A 10 year old girl with calcification of the twelfth thoracic and the first and second lumbar discs developed severe back pain. The lowest of the calcified discs were displaced into the adjacent vertebral bodies and projected posteriorly into the spinal cord. Three years later the lowermost calcified disc was found in adjacent soft tissues. Calcium had been absorbed from the others. Disc calcification in children was thought to be due to infection, since some have fever, leukocytosis and an elevated erythrocyte sedimentation rate.[2158] Among seven children with calcified discs, four had this in the thoracic region; none was displaced.[1908] A woman, aged 47, with calcification of the disc between the tenth and eleventh thoracic vertebrae, was hospitalized because of severe costal and sternal pain. After several months symptoms subsided and the calcified nucleus was located behind the eleventh thoracic vertebra.[2239]

Lumbar Discs. Many papers dealt with lumbar disc protrusions.[359, 722, 1363, 1503, 1580, 2006, 2033, 2043, 2127, 2228, 2271] The signs and symptoms were those discussed in previous reviews and were well known.[1084, 1772] Midline backache, either with or without sciatica, in a majority of instances was stated to be due to disc disorders.[1084] Nuclear protrusions were found to be most common in the lumbar region, and may provoke an osteophytic reaction on adjacent vertebrae. As a result, nuclear protrusions may be difficult to distinguish from annular protrusions.[252] Massive herniation only rarely affected lumbar discs but, when present, caused lancinating pains and numbness in the legs, also loss of sensations, motor power and sphincter control.[1084] Multiple protrusions of lumbar discs were found in 33 (16%) of 206 patients requiring operative treatment.[388]

Only five of 6,500 patients subjected to surgery for lumbar protrusions were under 16 years of age. However, this lesion could be the cause of persistent backache and sciatica in children.[2178] Herniation of intervertebral discs into congenitally narrow spinal canals of achondroplastic dwarfs caused compression of the cord or cauda equina, sometimes with progression to paraplegia when untreated. Two groups were described. In the first, a gradual onset of symptoms was caused by protrusion of multiple discs, while in the second, sudden onset of severe disability resulted from extrusion of a fragment of disc tissue. Myelography was helpful in localizing the level of compression.[641]

Diagnosis. Information concerning recognition of lumbar disc protrusions was based on previously widely disseminated data. A high index of suspicion was needed to assure adequate diagnosis of these conditions. The history, physical findings and roentgenograms were sufficient in some cases, but in others myelograms were needed to establish the diagnosis with certainty.[251, 453, 642, 989, 1016, 1084, 1503, 1540, 1547, 1578, 1700, 1772, 1774, 1869, 2264, 2278]

Frequent reference was made to the importance of differentiation of protruded discs from tumors of the cord and malignant tumors of vertebrae.[1084, 1549] Only two spinal cord tumors were encountered among 1,200 patients who under-

went operations for protruded discs. In this same period 19 patients with malignant tumors of bone presenting with symptoms and findings of disc protrusions included metastatic carcinoma of undetermined origin,[1192] osteochondroma not originating in discs,[247] and tuberculosis of discs.[157] Protrusions of thoracic discs may be difficult to distinguish from cord tumors, and also from intra-abdominal or thoracic diseases.[642] An unusual condition was described, characterized by symptoms of cauda equina compression, bilateral sciatica, disturbances of sensation and impaired strength of the lower extremities on standing or walking. These symptoms disappeared when the patients were recumbent. Myelography showed a blocking of the spinal fluid in the lumbar region in all. During surgical exploration, articular processes were found to be encroaching on the vertebral canal, with a resulting narrowing and compression of intraspinal structures.[2140]

Differentiation of sciatic pain of a referred type from sciatic pain due to root compression was often possible by utilization of the "bowstring" test. The test was carried out by having the patient sit on the edge of a table with his back held as straight as possible. The affected limb was then extended passively at the knee until pain appeared. It was then flexed slightly. The examiner then applied manual pressure in the popliteal space to the taut "bowstring" sciatic nerve. When a protruded disc was present this pressure on the nerve caused it to be tightened and pulled over the disc, causing pain in the back and the extremity.[512] Use of both electromyograms and myelograms resulted in a very high incidence of correct diagnoses in patients with disc protrusions.[2242]

Other ailments which may be confused with disc protrusion include sacro-iliac arthritis, arthritis of apophyseal joints, epidural varices, congenital anomalies of the spine, cysts of sacral nerve roots, fractures, infections of the spine, intrapelvic disease and carcinoma of the rectum.[1503] Cervical disc protrusion must be distinguished from cervical arthritis, scalenus anticus syndrome, cervical rib, costoclavicular syndrome, cord tumors and coronary artery disease.[1084, 1700]

Determinations of levels of spinal fluid protein and cerebrospinal fluid pressure may be of little aid in the recognition of disc protrusions. In one series, 15 of 32 patients with disc protrusions had normal levels of protein (less than 50 mg.%). In 12 the levels ranged from 50 to 90 mg.%; in three, between 90 and 134 mg%. In two the values were not determined. Cell counts, serology and the levels of sugar and chlorides were normal in all.[2278] Others reported similar experiences.[1084, 1323, 1540] Protein values in excess of 100 mg.% were observed in fewer than 10% of the patients. The finding of amounts greater than 100 mg.% suggested a need to test the spinal fluid dynamics, and should require the carrying out of myelography.[1084] An elevated level of spinal fluid protein suggested the presence of a tumor.[1323, 1774] Among 71 patients with disc protrusion proved by surgery, only 56% showed values of protein above the upper limit of normal. No correlations between spinal fluid protein level, site or extent of herniation, duration of symptoms or neurologic signs were found.[22] [Elevated spinal fluid proteins are found also in rheumatoid spondylitis. —Ed.]

Roentgen Examination. Roentgenograms often served to distinguish malignancy of the spine, fractures, infectious lesions, congenital defects, arthritis and osteoporosis from protruded discs.[1084] Anteroposterior, oblique and lateral views in the erect, flexed and extended positions aided in detecting protruded discs in the cervical region. A narrowed interspace did not necessarily indicate

a protruded disc, nor were narrowed intervertebral foramina necessarily indicative of compression of nerve roots.[251] Reversal or disappearance of the normal cervical spinal curve, narrowing of interspaces and posterior osteophytosis were at times associated with protrusion of cervical discs.[58, 380, 1016, 1540, 1578, 1700, 1869, 2278]

In the presence of late stages of lumbar disc degeneration, narrowed intervertebral spaces, sclerosis of adjacent vertebral margins and osteophytic lipping of vertebral bodies were seen. By means of films taken while the spine was flexed, early degenerative changes and abnormalities of apophyseal joints could be detected. Subluxations, chip fractures, degenerative arthritis and overriding of facets were also detected in this manner.[899] Anterior herniation of a nucleus beneath the epiphyseal ring may result in formation of a large osteophyte.[136] Roentgen examinations of the spine in lateral, dorsal and ventral flexion were said to give results superior to those obtained with routine examinations for diagnosis of disc protrusions.[1827] [It is difficult or impossible to evaluate this paper.—Ed.]

Discography. In some instances discography proved to be more accurate than was myelography in detecting protruding discs.[722, 727, 2246] A normal discogram was stated to be evidence against a diagnosis of disc protrusion.[2246] Transabdominal discography was carried out in 15 individuals during laparotomies. No complications referable to this procedure were encountered.[1609] During the procedure of injecting discs with Diodrast and procaine hydrochloride solution the patient may complain of pain when the needle perforates the longitudinal ligament and again when the cavity of a disc is distended by the solution. Such injections into normal discs usually caused only slight pain at the site of the injection. However, distention of a degenerated disc may accentuate the patient's symptoms. Roentgenograms taken immediately after such injections showed the interspace and sometimes showed a true cavity in the disc. Normal discograms showed only a central opacity.[722, 727]

Myelography. Recognition of disc protrusions was made possible in certain cases only with the aid of myelography. It was recognized, however, that this procedure may at times yield falsely negative results.[1323] Myelography was not recommended for routine use when protruding discs were suspected, but was reserved for those in whom the diagnosis was in doubt, or when it was desired to establish the level of a disc protrusion prior to surgery.[1084, 1503, 1700, 1774, 1869] In one series of 42 consecutive myelograms there were 15 false-positive and three false-negative examinations.[2033] Myelography gave more nearly accurate information concerning lesions in the cervical region than concerning those in the lumbosacral region. In one study of 32 patients, cervical myelograms showed central filling defects at more than one level in 30, and in only two patients were single defects seen.[2278] [Most of these patients appear to have had osteoarthritis or spondylosis rather than disc protrusions. —Ed.]

Myelograms were helpful in detecting lateral protrusions.[1869] Myelographic abnormalities characteristic of cervical disc protrusions included obliteration of roots and dural sleeves, indentations of the opaque column, abnormal transverse translucencies, median displacements of roots and sleeves, broadening of root shadows and root sleeve shadows, and upward displacement of roots and sleeves by pressure from below.[1700]

The procedure of lateral cervical myelography with fluoroscopic control was described. The column of Pantopaque was prevented from entering the skull by careful positioning of the patient and by the use of a tilt table.[1917] Air could be used as a contrast medium for easy, harmless and effective visualization of the cervical canal and cord. An intraspinal block may be demonstrated clearly by injecting 5.0 c.c. of air. Nonobstructing lesions may be demonstrated with 40 to 50 c.c. of air. A disadvantage was headache, from which patients often suffer when air enters the

ventricles and the subarachnoid space within the skull.[1506] When a lumbar disc protruded sufficiently to cause a filling defect or to involve a nerve root, symptoms were generally clearcut and myelography was not needed.[1869] One reason for false-negative findings was the posterior suspension of the subarachnoid sac. In many instances the anterior aspect of the sac lay so far posterior to the fourth and fifth lumbar interspaces and also to the fifth lumbar and first sacral segment interspaces that posterior protrusion of a disc did not demonstrably deform the sac.[727] Fourteen of 25 patients with cervical symptoms showed abnormal myelographic findings in the lumbar region, though none had symptoms of lumbar disc protrusion. This high incidence of falsely positive lumbar myelograms threw considerable doubt on the usefulness of the procedure for diagnosis of lumbar lesions.[2112]

Treatment of Protruded Discs. Some writers believed that "slipped discs" have been overemphasized. According to Friberg: "The operation still belongs to the realm of research surgery; the indications are not clear and the results cannot yet be evaluated. It may be that we are on the wrong track."[722] [This evaluation appears excessively cynical.—Ed.]

Enthusiasm for surgical treatment has ebbed. Only a small percentage of the cases required surgical treatment.[1428] Many expressed the view that conservative measures should be given a trial before patients with lumbar protrusions are submitted to surgery.[249, 256, 511, 776, 865, 1428, 1503, 1580, 1774, 2156, 2210, 2228] On the other hand, surgery was recommended without delay for thoracic and cervical discs with cord compression, and for large lumbar protrusions with compression of the cauda equina. These lesions were considered to have a poor prognosis, and the resulting disability was apt to be severe.[380, 642, 989, 1084, 1540, 1869]

Rest on a firm mattress, preferably in a flexed position, heat, analgesics and traction to the lower extremities were the essentials of conservative management for lumbar disc protrusions. Partial flexion of the knees and hips, with straightening or slight flexion of the lumbar spine, was thought to be helpful.[249, 511, 865, 1580, 1774] These measures were found to suffice for 85 to 90% of the patients.[1580] Massage, together with exercises for the back muscles and quadriceps, was considered to be of some help during acute episodes.[1503] Alternate periods of traction and release were more effective than was continuous traction.[2210] Traction applied to the lower extremities while the patient was fixed on a table was also said to be effective.[1371] An aluminum brace attached to hips, knees and feet by means of straps was helpful for applying traction to the lower extremities.[2156] The use of paravertebral injections with procaine gave satisfactory relief of acute sciatic pain in the majority of cases reported by Keet.[1102]

Success of manipulative treatments depended upon removal of pressures from nerve roots. In some instances, manipulation caused complete protrusion of a disc, aggravated symptoms and made surgery imperative.[776] Manipulations under anesthesia were carried out in 72 private patients and in 133 industrial patients. Satisfactory results were obtained in 64% of the private patients and in 45% of the industrial patients after one or at the most two manipulations.[1428] Ultrasonic treatments resulted in relief of pain in some patients, but this procedure was not curative.[2126]

At least 95% of patients with cervical disc protrusion could be managed by conservative measures.[700] Bed-rest, head traction, applications of moist heat, muscle relaxants, procaine hydrochloride infiltration of painful muscle areas and analgesics were useful measures during acute episodes.[380, 700] Differences in tolerance for pain and in emotional reactions to disability made each patient an individual prob-

lem.[1016] Head traction by means of a head halter should be carefully applied, with the cervical spine in slight flexion. Traction applied continuously for the first few days and later intermittently was better tolerated than was continuous traction.[380] Motorized intermittent traction for treatment of root pain due to cervical disc protrusion was recommended.[380, 1016, 1883] A collar designed to prevent hyperextension proved helpful for cervical protrusions. Such collars were more satisfactory and less expensive than braces.[700, 1016, 2068]

Sling traction applied to the head with the patient seated was tested in patients suspected of having protrusion of cervical discs. The amount of traction ranged from 30 to 100 pounds, depending upon the patient's ability to relax during application. The average patient was treated with 60 pounds of traction for from one to three minutes, and treatments were given twice daily. Forty-one (67%) showed initial definite improvement. Six months to five years later 47 (77%) were still notably improved, two slightly improved, and 12 (19.7%) had undergone surgery. None who had immediate relief required surgery; however, several had experienced recurrences and were again relieved by conservative management.[1358, 1359] One objection to vertical traction was the inability of some patients to relax while in a sitting position.[2016] Cortisone, phenylbutazone and Thorazine and, rarely, opiates were recommended for pain.[1016] [We see no indication for corticosteroids in patients with disc herniation.—Ed.]

Surgical treatment of a protruding lumbar disc was an elective procedure, indicated for severe pain persisting despite conservative management for recurring sciatica, for progressive muscular weakness and increasing sensory loss, and in instances where, for economic reasons, a patient could not continue conservative therapy for a prolonged period.[776, 865, 1458, 1503, 1580, 1869] Large extrusions which caused severe pain demanded removal by surgical means without delay.[1869]

During the period of this review, relatively little was written on the subject of the surgical technic of disc removal. A retroperitoneal, transabdominal approach was described, and it was suggested that disc removal be preceded by discograms made using an anterior approach.[1259] Among 206 patients subjected to operation for lumbar discs, 33 were found to have multiple protrusions.[388] Satisfactory relief of pain and restoration to normal working capacity were achieved in 90% of patients from whom protruded discs were removed surgically. Spinal fusion was done at a later date in those patients whose spines failed to stabilize after the disc was removed.[2043] [The procedure is by no means uniformly successful in producing pain relief in those with back pain after disc excision.—Ed.] A number of writers objected to the combined operation of disc removal and spinal fusion.[511, 776, 1851, 2043] One writer reported that he had employed fusion in addition to disc removal in 20 of 113 cases. Indications for the combined procedure included hemilaminectomy or total laminectomy performed for removal of the disc, spondylolisthesis, spina bifida, sacralization of a transverse process with a false joint, bony osteophytes, marginal sclerosis of bony surfaces just above or below the disc area, and an unstable fifth lumbar vertebra observed and proved at operation.[1851] Two groups of patients followed over periods ranging from six to 10 years were studied to determine the relative values of disc removal alone, and disc removal combined with spinal fusion. Good results were obtained after the combined operation more frequently than after disc removal alone. Chances of a complete failure were 10% greater when fusion was omitted. The combined operation required a longer period of hospitalization and convalescence but produced better results.[2271] The best results were obtained in those having acute pain at the time of operation. Ten year follow-up studies comparing surgical and nonsurgical treatment showed little advantage for surgical therapy of lumbar disc protrusions.[1084]

A study of patients who had unsatisfactory results from surgery showed that

these failures resulted from incomplete removal of degenerated nuclear material, failure to recognize multiple protrusions, trauma to nerve roots at the time of operation, incorrect diagnoses, tears in the theca with formation of meningoceles, and failure to recognize degenerated discs at operation.[1062] Other causes for postoperative complications included postoperative formation of scars about the dural sac and nerve roots, intraneural scar formation, infections in the disc spaces and arachnoiditis. The most frequent complication was formation of a scar about dural sacs and nerve roots.[776]

Cervical and thoracic disc protrusions involving the spinal cord indicated sugery as soon as possible, inasmuch as the prognosis and the rate of permanent disability were high with conservative treatment.[642, 989, 1084, 1869, 2264] Only in cases where the protrusion was lateral was it considered advisable for the patient to be treated conservatively for a time.[642, 2264]

Regional anesthesia for surgical removal of protruded cervical discs was preferred to general anesthesia.[1095, 1869] A thorough exploration for a distance of one and one-half to two laminae above and below the lesion was agreed upon.[1540, 1869, 2278]

Sciatica

The time-honored term "sciatica" was regarded as descriptive and useful. It was not a diagnostic term, and its use as such was not condoned. The concept of toxic or infectious sciatic neuritis has lost ground in recent years and was mentioned rarely.[495] Sciatica or pain over the course or distribution of the sciatic nerve was usually caused by one of two mechanisms. The resulting two types of sciatica are unlike in some ways and can usually be differentiated.

The first is the root compression syndrome, caused by encroachment of any structure, such as a protruded disc, proliferated synovia of an apophyseal joint, posterior osteophyte, cord tumor or any inflammatory lesion, on a nerve root, usually in the region of an intervertebral foramen. Pain arising from compression of a nerve root, so-called radicular pain, was described as aching, boring, burning, lancinating or shooting, and was associated with paresthesias described as prickling, tingling, numbness, a feeling that the part is "dead" or "asleep" or the sensation of a tight band. Hyperesthesia, hypesthesia or distortion of sensation when the skin was touched was a common complaint. Motor weakness, together with atrophy, fasciculation and fibrillation of the muscles, also occurred. The distribution of symptoms in radicular lesions follows a nerve root pattern. Symptoms and findings were generally limited to a small portion of the total area supplied by an affected nerve. Pain was often widespread in the proximal portion of distribution of the nerve and limited peripherally. Paresthesias were usually more prominent in the peripheral regions supplied by the nerve root. Coughing, sneezing or straining at stool initiated or aggravated the root pain. Pain which increased at night and characteristically awakened the patient between 2 and 4 a.m. frequently was radicular in origin and was sometimes due to a spinal cord tumor. Some patients had to sit up to sleep, and some obtained relief only by walking. Traction on the involved root was said to be due to the increased body length which follows a period of recumbency. Stretching of the nerve root was also responsible for initiation or aggravation of root pain by straight leg raising or flexion of the neck.[273]

The second type was the referred sciatica due to irritation of the nerve endings of the posterior branches of lumbar and sacral nerve roots which innervate

the joints and deep structures of the back and the meninges. Apophyseal joint pathology, myositis, fibrositis, protruded disc, degeneration and irritation of the posterior longitudinal ligament, inflammatory conditions (tuberculosis, undulant fever, typhoid fever) involving bones and joints of the low back, tumors, herpes zoster and mechanical disturbances of the low back may result in sciatic pain. The point of origin need not be in the back. Direct irritation of the sciatic nerve in its peripheral course or lesions in its area of innervation other than the back, such as trochanteric bursitis or iliopsoas tendinitis or a pelvic lesion, may result in sciatica.[511, 512] The "irritative" type or referred type of sciatic pain may be quite diffuse, and may spread into the buttocks, or extend down the posterior aspect of one or both thighs to the knee or occasionally to the foot or toes.[511] [These two types of sciatica are frequently not clear-cut.—Ed.] Weakness of muscles, evidence of atrophy and reflex changes were seldom seen.[10]

A careful history and physical findings usually furnished a lead as to the cause of sciatic pain. The root pain of the compression syndrome may be aggravated or produced by jugular compression, hyperextension of the back with the patient lying in a prone position, straight-leg raising and the sciatic tension test.[512] [This test, also known as the "bowstring test," is described under the heading of "Diagnosis" in the Disc Section.—Ed.] Mechanical causes, ankylosing spondylitis and other types of arthritis were found to be responsible for much of the referred sciatica.[256, 512, 722, 2014]

In this referred type or "root irritation syndrome," muscle atrophy and reflex changes were described as absent or slight.[10] However, a diminished ankle jerk was mentioned as a finding in sciatica due to transitional lumbar vertebra.[2014] Sciatica associated with spondylolisthesis was more frequently of the reflex type than of the root compression type, and physical signs or reflex changes were seldom found.[10] Coexistence of a benign cauda equina neoplasm and spondylolisthesis in a patient with sciatica was reported.[1085] An unusual cause of sciatica was endometriosis involving the sciatic nerve.[503] Polyneuritis and radiculitis associated with multiple myeloma were attributed to a toxic effect of some type, as no evidence of direct nerve involvement either by tumor or by bone collapse could be found.[645] Four proved cases and one probable case of sacral and lumbar cysts were reported as causing back pain and sciatica. Myelography was not conclusive. Unroofing of the sacrum was recommended in those cases where exploration of the back was negative.[2035] Guillain-Barré syndrome was considered to be a special form of radiculitis.[273] A patient with chronic sciatica and thyrotoxicosis was said to have been relieved completely of sciatic pain after the thyrotoxicosis had been treated.[185]

The term "neuritic" sciatica was used to include the idea of inflammatory and "endotoxic" neuritis, such as is seen in diabetes mellitus and pregnancy. Involvement was usually unilateral; reflexes were seldom altered; muscles were painful; the course was favorable and short, and no evidence of a disc protrusion was found on myelography.[495]

Gout and Gouty Arthritis

Careful accumulation of clinical data and application of reasonable, well founded principles of management have altered previously accepted concepts of the course and prognosis in this disease. With modern investigative technics,

some of the enigma clouding the nature of gout is being cleared away. More recent knowledge of the metabolic abnormalities in gout obtained by these methods complements the results of long-term treatment with urate-mobilizing agents. Increased alertness to the identification of the individual with gout, and application of present-day principles and agents of treatment, were advisable, for with these advances acute suffering could be quickly relieved and held in abeyance; furthermore, it appears well established that by long-term administration of uricosuric agents the stigmata of chronic tophaceous gout may be checked and often reversed.

Significance, Incidence and Clinical Data. The impact of gout upon the lives of notable personalities was apparent in selected, well written accounts.[193, 828, 2057] A painstaking history of colchicine has appeared,[925] as has an account[1041] of the use of salicylates in this venerable disease. Very little new information has been obtained with respect to the incidence of gout. Of 12,000,000 arthritics in the United States, 4% (480,000) were estimated to have gout;[1948] reliable data were lacking as to the true world incidence of the disease.[2056]

Although few pure-blooded Negroes of African descent were reported with the disease,[2056] a second case of tophaceous gout was recorded in a Negro woman.[107] In a series[103] of 450 cases of gout from the eastern part of the United States, 12% were of Italian descent; other nationalities were evenly affected. The sex ratio in gout was approximately 20:1 in favor of males;[103, 2055] less than 5% of the gouty patients seen by Talbott[2056] were women. By contrast, Kuzell[1188] reported that, of 504 patients with primary gout, 74% were males and 26% were females. [This author's diagnostic criteria are not acceptable to many of us.—Ed.] Note was again made that women with gout had a low fertility rate,[2056] and that symptoms not uncommonly followed an artificial or a natural menopause.

Although a few individuals had trouble as early as the first decade of life[323, 1704] and others as late as the eighth, the majority[2056] of individuals had their first attack between the ages of 20 and 40, or[103, 1188] in the fourth or fifth decade. The earlier in life the first attack of gout appeared, the more severe the disease was apt to be.[2056] That gout may begin at any age was illustrated in the history of a vegetarian with known hyperuricemia for three years who experienced the first attack of gouty arthritis at 81.[2055]

Frequency of Tophi. Although the patient's age and duration of symptoms were generally related to local deposition of urates, there were certainly other, unknown factors influencing the appearance of tophi. They rarely appeared before articular manifestations.[1315] [Some of us have observed this too.—Ed.] In one series of 504 patients with primary gout[1188] the incidence of tophi was 13% in males and 3.8% in females. Sixty per cent of visible tophi were observed in patients whose gout had been symptomatic for more than 10 years. In a second large series[103] of 450 cases, tophi were observed in 21%; they were noted at multiple sites in 30%, in the ears alone in 43%, and with tophi elsewhere but not on the ears in 15%. Eighty-eight per cent of the patients with tophi had had gout for more than six years; by contrast, 50% of those individuals who had no tophi had had gout for more than 15 years. [Talbott[2058] has recently reported that in a large series less than 25% had tophi in the ears or about affected

joints.—Ed.] Others[43] reported an incidence approaching 40%, or as low as 16.8%.[1188] [Variation in incidence of tophi reflects in some measure the diagnostic criteria used.—Ed.]

Incidental Associations. Nonspecific features observed in a large series[1188] of gouty patients included the ruddy color and tendency to plethora, hyperactivity, chalklike deposits in nails, and "characteristic body odor"; muscle atrophy was usually absent; ankylosis is rare. Other diseases coincident with primary gout included obesity (present in half of the males and females), hypertension (present in one fourth of the males and one third of the females), and cardiac disorders (in 10.7% of the males and 1.5% of the females). Alcoholism was relatively uncommon in these patients. In a second large series,[103] common coincidental diseases were obesity (23%), hypertension (9%), and coronary heart disease (9%); 33% of the group were heavy drinkers. The association of gout with osteogenesis imperfecta tarda was reported for the first time[28] in three cases that appeared to be on the basis of a chance genetic relationship of two separate famial diseases. The association of gout and acute thrombophlebitis was discussed.[513]

Secondary Gout. There has been little further information concerning secondary gout since this concept was emphasized by Gutman.[1] "Secondary gout" may occasionally occur in the course of primary or secondary polycythemia, myeloid metaplasia, chronic leukemia, chronic hemolytic anemia (including Cooley's anemia in adults), pernicious anemia and malignant lymphomas; it rarely if ever was found to be associated with the hyperuricemia of chronic nephritis. Acute gouty arthritis secondary to unsuspected multiple myeloma was reported.[269]

In some instances[1188] acute gout may be the first manifestation of the underlying hematopoietic disorder. That overt gout in these circumstances does not always represent a chance occurrence of primary gout was substantiated[856] by the 5 to 9% incidence of gout with the hyperuricemia of polycythemia; moreover, there was often a distinct temporal relationship to radiation or chemotherapy. The familial occurrence of gout in such subjects was conspicuous. [This is a point calling for careful study.—Ed.] The mechanism of this form of gout was believed[856] to be due to "liberation into the blood of a plethora of intermediary purines, including the metabolic end product, uric acid." Labeled glycine studies supported this theory.[2277] Acute intermittent gouty arthritis superimposed upon rheumatoid arthritis while the patient was under prolonged treatment with cortisone was again mentioned.[1188] [Not verified. This combination of diseases is very rare.—Ed.]

Provocative Factors. Although it was agreed that the inciting agent should be searched for after each attack of gout, it was true that in many instances neither the patient nor the physician was successful in identifying these agents.[2058, 2060] Provocative factors were classified[1777] as physical, occupational and psychologic. The susceptibility of the severely afflicted gouty joint to minor cutaneous stimuli was particularly stressed.[2060] This related to tight fitting or the rapid breaking in of stiff new shoes, unusual exertion associated with sporadic participation in sports or hobbies,[1777] and long automobile or aeroplane rides. An acute bacterial infection may be the offender.[2056] Drugs capable of provoking acute gouty arthritis included penicillin, which was thought to prolong symptoms in an inadequately treated attack, as well as to incite other joints to acute activity. [Other antibacterials—namely, pyrazinamide[791]—also may induce attacks of gouty arthritis.—Ed.] In patients with diabetes and gout, acute attacks followed promptly after episodes of hypoglycemia,[2058] but employment of therapeutic agents to provoke deliberately an acute attack of gouty arthritis was rarely mentioned.[1188]

Factor of Heredity. No explanation for the cause of the disease was acceptable unless it accounted for a familial tendency to hyperuricemia.[978] In the most recent

investigation [930] of the concept that hyperuricemia is the genetic factor in gout, study of relatives of 32 individuals with gout supported the theory that heredity is an etiologic factor because hyperuricemia was more common among the relatives of gouty patients than in the general population. The investigation did not, however, "appear to support the view that hyperuricemia is transmitted as a mendelian dominant." The results indicated that dominance with incomplete penetrance and recessive heredity was excluded, but that accumulative gene action (polymerism) may be operative. [We agree that there is probably little to be gained by continued studies of serum urate levels in relatives of patients with gout. When it becomes possible, more will probably be gained by studying the individual steps of uric acid synthesis as well as its excretion in the individuals of afflicted families.—Ed.] Factors influencing the transition from the genetic carrier to frank clinical manifestations remained unknown.[2287] Severe gout in prepuberal boys and in young women was often associated with a strong familial history of gout.[2261] The familial incidence of gout varied from 23% [103] to approximately 50% [1947] to as high as 75 or 85%: "there are instances in which the disease skips a generation or appears in an uncle or a cousin rather than through a direct line." [2056]

Pathogenesis of Hyperuricemia. The theories explaining the mechanism of hyperuricemia still included overproduction, specific impairment of renal excretion, and diminished destruction of uric acid. With respect to the adequacy of renal excretion of uric acid, Gutman [855] pointed out "that the development of positive uric acid balance in gout may in a sense be due in part to a perversity of renal function." Why the normal kidney so sedulously, by efficient tubular reabsorption, preserves the apparently useless uric acid, the end product of metabolism in man, was not clear. "This reabsorptive activity, paradoxically, is generally preserved in gout; it may, in fact, be relatively increased." The increased importance of persistent tubular reabsorption in the face of degenerative vascular changes (impairing the efficiency of glomerular filtration of uric acid) was pointed out as favoring uric acid deposition in the kidneys and tissues. Wyngaarden [2261] pointed out that specific impairment of urate excretion as a cause of hyperuricemia in patients without complicated gout appeared to be outweighed by contrasting evidence. Furthermore, according to this author, there was no information to indicate whether uricolysis plays any significant role in the metabolic defect in gout. [Additional evidence derived from studies of labeled uric acid supports the presumption that there is an increased formation of uric acid in the gouty subject, and refutes indirectly the etiologic theory that gout is caused by a differential impairment of renal function.[2058] Recent metabolic studies dealing with the pathogenesis of hyperuricemia are discussed in detail under The Uric Acid Problem.—Ed.]

Pathogenesis of Acute and Chronic Gout. Speculation continued [216, 973] that temporary relative adrenal cortical deficiency or diminished target responsiveness may be implicated in the pathogenesis of the acute seizures. It was generally agreed that hyperuricemia is usually (98%) present.[1947] [One of us (H. F. P.) thinks this percentage is too high.—Ed.] In general, serum urate concentration bore no relation to the severity [2057] or the duration of gout.[103] Although fluctuation in uric acid values was not generally believed to be related to the onset of acute attacks, one study [103] revealed that during an attack the urate level was in excess of 6 mg.% in 58% and between attacks in 88%. The onset of acute gouty arthritis with initiation of uricosuric agents therapeutically

has emphasized the seemingly paradoxic relation which may exist between serum urate levels and acute gouty arthritis. Marson[1356, 1355] pointed out that attacks could occur regularly at a time when the blood level had been brought to normal. It was speculated that the uric acid level in the tissue fluid in proximity to the dissolving tophi was appreciably higher than the level in the serum. Mason[1367] emphasized that if we could elucidate the reason why these attacks occur we should be nearer an understanding of the acute attack, and speculated that uric acid per se was not responsible for the acute paroxysms, but that there was perhaps an abnormal precursor of uric acid which was responsible for the acute attack, the formation of which may be blocked with colchicine. Some[973] expressed the opinion that the acute attack was probably induced by the sudden precipitation of sodium urate in and around joints, and by an exaggerated inflammatory response to this precipitation; it appeared as though the crystals acted as seed for further acute deposition. [In this respect, it is of interest that synovial biopsy has established the presence of urate crystals in the synovial tissues of acute gouty arthritis not uncommonly, as pointed out by Polley in 1951 and recently confirmed.[1957, 2288]—Ed.] On the other hand, in Gutman's opinion,[855] "Acute and chronic gouty arthritis both ultimately derive from a common error of purine metabolism; but, it seems probable that different immediate mechanisms, operating within the general framework of the overall metabolic anomaly, are responsible for these two expressions of the gouty trait. Despite the general assumption, the episodic, fulminating local and systemic manifestations of acute gouty arthritis probably are not due to uric acid, per se, a pharmacologically inert substance." [In other words, we are still in the realm of speculation regarding the pathogenesis of acute gouty arthritis.—Ed.]

Chronic gouty arthritis, it was generally agreed,[855, 1948] was the direct result of deposition of uric acid and structural derangement in joints. Although ". . . it is often difficult in tophaceous gout to distinguish between minor attacks and exacerbations of chronic secondary inflammatory reactions, . . . chronic gouty arthritis cannot be regarded simply as protracted acute gouty arthritis or as the cumulative result of repetitive acute attacks, since in many cases, tophi form without preliminary acute manifestations in the area of deposit. Moreover, . . . uric acid frequently is deposited in nonarticular cartilage (ear) and may accumulate in viscera, notably the kidneys. Chronic gouty arthritis is therefore but one aspect of a more general, if still selective, trend toward increment of tissue uric acid with the passage of time."[855]

Laboratory Data. There were other pathologic states besides gout[1948] producing hyperuricemia, such as leukemia, lymphoma, polycythemia and poisoning by ammonia, barbital, carbon monoxide and methyl alcohol. The relatively low incidence of gout in these conditions was considered as possibly indicating that the elevated serum urate is not by itself the cause of urate deposition in the tissues.[1403] The most common cause[2261] of hyperuricemia was renal insufficiency; urate retention might precede that of urea or creatinine; values as high as 27 mg.% have been observed in uremic individuals, although concentrations of 15 mg.% were unusual; the ingestion of purine-rich foods by such subjects might be followed by an increase of serum urate concentration.

Whether the serum urate is always elevated during the first few attacks was again debated.[1188, 1367, 1947, 2055] [In this respect, it is essential to know whether ingestion of various uricosuric agents (salicylates, probenecid, phenylbutazone, corti-

cotropin, cortisone, hydrocortisone, prednisone, zoxazolamine (Flexin) and cinchophen) has occurred in the 24 to 48 hours preceding estimation of serum urate values.—Ed.] Talbott [2058] advises that the concentration of uric acid in the serum should be used to confirm rather than to make the diagnosis in the absence of characteristic clinical findings. Serum urate values in gout were reported [2261] to rise as high as 12 to 15 mg. per 100 ml., though seldom higher.

The usual methods for determination of blood uric acid depended upon the reduction of complex tungstate reagents to colored compounds; this was not strictly specific for uric acid, and results were influenced by unrelated substances present in blood. Determination of uric acid values on whole blood was considered inadvisable, since there is unequal distribution of urate between plasma and cells. Only the use of carefully prepared and fresh reagents and frequent control determinations assured reliable results.[1392] Evaluations were reported of serum urate determination by an ultramicro carbonate method [335] and by the uricase method.[661, 1188] According to Wyngaarden,[2261] the most commonly employed procedures (Folin or Benedict) were associated with inaccuracies, on the low side primarily, because preliminary precipitation of plasma protein was involved. The method of Praetorius, based on the change in ultraviolet absorption when uric acid in diluted serum is acted upon by highly purified uricase, was specific for uric acid. Although technical difficulties prevent its common usage, it has served as a valuable criterion for the evaluation of colorimetric methods. [An excellent discussion of the quantitative analysis of uric acid in blood and urine by Yü and Gutman [2276] has recently been published.—Ed.] Since most of the methods [2261] for uric acid yield values which are too high when applied to urine (because of nonuric-acid-reducing substances), use of combined uricase colorimetric methods or of the uricase differential spectrophotometric method was advised.

The paradoxic effect of uricosuric drugs (probenecid, salicylates, phenylbutazone and its derivatives), whereby large doses increase and small doses suppress renal excretion of uric acid, was clearly demonstrated by Yü and Gutman.[2275] It was concluded that "the capacity to cause uric acid retention when given in low dosages is to a greater or less degree a property common to uricosuric agents." A marked tendency to high "athrogenic" indices was reported [1188] in gouty individuals; the ratio of reduced to total blood glutathione was in general elevated. Development of fatal hypoglycemia with decrease in blood uric acid and total nonprotein nitrogen was described [1273] in fasting hypophysectomized pigs; these findings were in contrast to those observed under the same circumstances in the nonfasting animal. [The very interesting observation has recently been made [791] that the antituberculous agent, pyrazinamide, may provoke hyperuricemia and occasionally acute gout, associated, curiously enough, with decreased urinary urate excretion. The new and extensively used oral mercurial diuretic and antihypertensive agent chlorothiazide (Diuril) also may produce hyperuricemia.[1712]—Ed.]

Pathology. The value of the punch biopsy technic in the diagnosis of gout by demonstration of urates in tissue was pointed out.[668, 1649] [Recent and more extensive studies have confirmed these observations.[1957, 1288]—Ed.] In some instances this material indicated that precipitation of urate crystals apparently occurred in the synovia during an acute attack [or before.—Ed.] The possibility of studying gout by examination of the sternoclavicular articulation at autopsy was stressed,[1958] and material so obtained was described. The paucity of autopsy material in this disease was indicated by the report [2108] of but one necropsy in a patient with gout in 10,036 autopsies in about a seven-year period at a large city hospital. In this and an additional case the claim was made that urates occurred in the arteries, in or on the valves and muscles of the heart ("visceral gout"),

and in the intima of arteries or in organized thrombi. The necessity for careful scrutiny of the viscera in bodies that show evidence of joint disease was stressed; absolute alcohol, of course, should be used as the fixing solution for tissues in which urates are being sought.

The significance of vascular sclerosis in gouty patients and its relation to hypertension were emphasized;[1330] a patient who had had gout for from 15 to 20 years almost invariably developed generalized vascular damage, and the kidney was a favorite site. "In the third stage of chronic gouty arthritis visceral lesions are apt to determine the clinical picture. Arteriosclerosis is often present and for many patients appears to have an accelerated course."[1777] Ropes[884] pointed out that the uric acid deposition in the kidney played at the most only a small part in the renal impairment as a rule, and that most often the process in the kidneys was severe nephrosclerosis. The increased prevalence of arteriosclerosis, especially in the kidney, and of hypertension in gouty patients remained an unsolved problem.

Prognosis

Talbott[2057] emphasized optimism with respect to present-day prognosis in gout. "With the earlier and increased recognition, the proportion of those severely afflicted has decreased significantly." Of those individuals seen by him in the last decade, "it is believed that not more than 2 or 3% have died or will die prematurely because of the disease. More than 90% of those afflicted suffer surprisingly little and are able to lead normal lives." In his experience, premature death in patients with gout usually was associated with renal disease. The only patients with gout who have died in the group followed by him during the last eight years have had irreparable renal involvement or have died from some unrelated malady, such as a malignancy. Life expectancy for most patients with gout was unaltered by the presence of the disease. In fact, the conscientious gout patient may have an augmented life expectancy. The recognition afforded this malady by the actuaries of life insurance companies was encouraging. Ungerleider,[2120] in discussing changing concepts of mortality of disease based upon statistical evidence, stated: "Mortality in gout was shown to be normal."

Diagnosis

Early identification and institution of proper long-term treatment were considered to be of vital importance[1948] in the prevention of painful, crippling joint deformity and the fatal renal and vascular complications of gout. Two dramatic case reports of severe mutilating tophaceous gout illustrated the importance of early and correct diagnosis; in one instance[328] the first manifestations of the disease were observed in a boy at the age of 12 in whom definite tophi were present at 21; in the second case[1704] the onset of joint pain and swelling began in a Danish girl at the age of five; ulcerating tophi required amputations 18 years later. The diagnosis of gout was frequently missed. In Bartels' series of 450 cases[103] the diagnosis had been made in somewhat more than half of the patients. In another series[1815] of 20 patients, the diagnosis had been overlooked or unduly delayed in eight patients for from two to 12 years; four of these had tophi, and six had podagra; an average of 11 attacks of gout had occurred in seven of these individuals. In a three-year period in an arthritis clinic in the

southern United States,[1392] seven individuals were discovered who were receiving therapy directed against rheumatoid arthritis but who had the unmistakable stigmata of gout. From England came the observation[1367] that it was "indeed remarkable how often the diagnosis of gout is missed and perhaps more frequently a diagnosis of gout is made where some other condition exists." [We agree.—Ed.]

Criteria for Diagnosis. Diagnostic criteria were again noted to be extremely variable, and there was no agreement regarding exactly which criteria are essential.[1948] Clinical evidence pointing to the diagnosis[2057] (which may precede by several years the first attack of acute articular distress) included: the history of a urate stone, a family history of gout, transitory albuminuria or moderate hypertension and, according to another observer,[1188] a family or a personal history of diabetes. The essential clinical features upon which rests the diagnosis of presumptive gout continued to be:[1948] "the characteristic clinical course, hyperuricemia and typical response to colchicine. The striking similarity of the symptom complex makes the history of this unvarying pattern a reliable part of the diagnosis." In acute bouts, the resemblance to extensive cellulitis with a systemic reaction with fever to 101° F. or higher and leukocytosis was again emphasized.[2056, 2196] Although the first attack frequently was found to involve the metatarsophalangeal joint of the great toe, any joint peripheral to the shoulders and hips may be involved; acute gouty arthritis of the hips, sacro-iliac joints, shoulder or spine was not observed[2056] except in well developed cases where there was no doubt about the diagnosis. Data have been gathered,[108] based on a careful study of a large series of patients, referring to the site and duration of the initial and subsequent attacks of gout. If proper treatment was carried out, return of joint function may be complete in 24 or 36 hours; if delayed, acute attacks may smoulder for days, weeks or even months.[2056] [Many physicians are not aware that prolonged, acute attacks lasting several weeks do occur in the intermittent stage of the disease, especially if therapy is inadequate.—Ed.] Since the first complaint may be nonarticular, it was suggested[1188] that all patients complaining of nontraumatic musculoskeletal discomfort should have at least one serum urate determination; the presence of advanced degenerative arthritis, acute peritendonitis or bursitis should suggest the possibility of gout. The conditions most commonly mistaken for acute gouty arthritis were listed as acute rheumatic fever, acute septic arthritis or cellulitis, and atypical rheumatoid arthritis.[1948] In women,[1392] gout was reported to assume atypical forms, frequently superficially resembling rheumatoid arthritis. [Gout is still rare in females.—Ed.]

Therapeutic response to colchicine has withstood the test of time as well as any other criteria for the diagnosis of gout. A delay in such treatment[2057] of even a few hours after the onset of the acute attack may be associated with decreased response to colchicine and may make the therapeutic test less reliable. Furthermore, it was not generally appreciated that a superimposed attack on chronically damaged joints may not entirely subside with the first course of colchicine; in these instances, the response to the drug may be less dramatic and often incomplete.

Course. Descriptive terminology varied with respect to the course of gout. Smyth[1948] described three stages: asymptomatic hyperuricemia ("larval gout" of Hench), acute intermittent gouty arthritis, and chronic gouty arthritis. Mason[1867] divided the disease into four stages: asymptomatic hyperuricemia, acute nonarticular attacks, polyarticular attacks with complete remissions, and chronic gout. Talbott[2057] spoke of acute gouty arthritis, the intercritical period, and chronic gout. It was generally agreed[1948] that the stage of asymptomatic hyperuricemia may antedate for some time the acute attack. All of these individuals do not develop gout; several of the nonaffected relatives in Talbott's series[2055] have had elevated serum uric acid

for more than 15 years without clinically evident signs of gout. The intercritical period between the first and second attack usually lasts for from one to two years. [Often, if gout is severe, the interval between the first and the subsequent acute bouts is only a few months.—Ed.] Younger patients were more apt to go through all three stages;[43] chronic gout might not occur if acute gouty arthritis did not develop until later in life.

Chronic gouty arthritis or tophaceous gout represented the tissue reaction to deposits of urate crystals. At the initial examination[1188] it was considered advisable to obtain x-rays of the feet and ankles, looking for the characteristic "punched-out areas" in subchondral bone or near the joint margin which do not have areas of sclerosis surrounding them, as do cystic areas in osteoarthritis or rheumatoid arthritis. [In many cases the lytic areas seen in roentgenograms of bone in gout cannot be differentiated from the cystic areas of rheumatoid arthritis.—Ed.] Occasionally, the punched-out areas actually erode into a joint or through the cortex of the shaft of a phalanx, producing a bony defect. As destruction increased,[1948] reduction of joint space occurred. Further extension produced complete obliteration of the joint, sclerosis of bone and secondary hypertrophic spur formation. Tophi were opaque only when there had been secondary deposits of calcium.[1188] Tophi and other subcutaneous urate deposits were occasionally associated with periosteal calcium deposits or generalized calcinosis.[1392] Bartels[103] observed x-ray findings compatible with gout in only 15% of his series. The x-ray findings described as "typical" for gout needed to be distinguished[43] from changes observed in rheumatoid arthritis, sarcoidosis, syphilis, hyperparathyroidism, Kaposi's sarcoma[1766] and multiple myeloma.[1642] [The aphorism of Hench—a tophus is never a tophus until urate crystals have been demonstrated—should be kept in mind.—Ed.]

Treatment

Bartels[103] stated that there are undoubtedly some patients in whom, decade by decade, the disease does not progress in a detectable manner and in whom it makes little difference what dietary or therapeutic regimen is followed. However, attainment of a normal life for the majority of gouty subjects is based on the premise of complete control of the disease.[103] Although it remained to be demonstrated that the full use of available drugs would satisfactorily control the disease in a large proportion of the cases,[1367] this was agreed to be the goal of therapy. To achieve this a close degree of coöperation is required between the physician and the patient. Complete control of gout implies careful and repeated observations by the physician of the course the disease is taking.

Acute Attacks. There was general agreement that the cardinal principle in management of the acute attack was employment of the most effective agent to achieve rapid relief of pain and restoration of normal joint function. Symptomatic relief of the acute attack was not dependent upon alteration of the concentration of serum urate; colchicine, which had no known effect on serum urate levels, was still the agent par excellence for the acute attack. [In spite of this fact, it is unfortunately still true that the uricosuric agent, probenecid, continues to be administered, without colchicine, in acute attacks of gout—and sometimes with disastrous results.—Ed.]

General Measures. The effectiveness of salicylates in the acute attack of gout was disputed,[280, 1777, 2155, 2196] routine use was certainly not satisfactory to control the pain of the acute attack. Although most authorities agreed that there was little to be gained, at the time of the acute attack, by altering the diet,[103, 2057] others[1777] advised a diet as free of purines as practical. A high fluid intake, especially in the

presence of fever, was recommended, and early ambulation was encouraged. [Weight bearing may prolong the attack.—Ed.]

Colchicine. Although colchicine is specific for acute gouty arthritis and exerts no dramatic action upon other types of articular disease,[2057] it was not generally appreciated[103] that this drug must be started at the very onset of an attack. The patient should have colchicine tablets available at all times in order that ingestion may be started with the first twinges of joint pain. Oral preparations (0.5 to 0.6 mg. tablets) were considered to be preferable. For the mild attack, not more than three to four doses (1.0 mg. every two hours) were recommended; if the attack was severe, ingestion of colchicine was continued without interruption, irrespective of the time of day or night. Oral colchicine failed to produce optimal relief if the full course (10 to 14 tablets for some patients) was interrupted by a lapse of several hours. If the acute attack failed to respond completely, a second full course after a lapse of two or three days was then in order. If the joint distress did not respond following a second full course, review of the diagnosis or a complicating factor was considered. Although development of colchicine "fastness" was mentioned,[1188, 2000] most observers were in agreement that, in patients on prophylactic colchicine for long periods, intolerance to the drug during an acute attack has not been observed. The nature and incidence of toxicity to colchicine were summarized.[1188] The successful use of ACTH to overcome hypersensitivity to colchicine was described.[2243] Reference was made[1117] to a fatality associated with colchicine, apparently on the basis of hypersensitivity, where there was massive necrosis of germinal centers of lymph nodes.

Intravenous colchine was reported to be effective and was particularly advantageous when oral colchicine was not well tolerated or could not be employed. For routine use, when feasible, the first dose of colchicine (0.5 mg. to 3.0 mg. in 5 ml. of distilled water) may be given intravenously. [Rarely necessary, and inadvisable if oral route can be used.—Ed.] Reports of clinical experience with intravenous colchicine[103, 1188] included[269, 489] description of two cases of gastrointestinal hemorrhage. Severe thrombophlebitis with extravasation after administration of intravenous colchicine was also reported.[1188]

An analogue of colchicine, desacetylmethylcolchicine (demecolcine, Colcemide), produced complete remission within 48 hours in 15 of 20 patients following intravenous administration of from 1 to 4 mg. of this preparation;[1186, 1188] side-effects were minimal. Satisfactory results also were generally obtained[417] after a total oral dose of from 5 to 8 mg. [A recent report of alopecia associated with administration of desacetylmethylcolchicine stresses the potential toxicity of this agent.[1448] Instances of granulocytopenia with anemia have also developed. Additional clinical investigation of this new agent is necessary to determine its safety.—Ed.]

Phenylbutazone. About 10% failure to respond to phenylbutazone was reported.[486] A case was mentioned[541] where phenylbutazone appeared to intensify the gout. Aside from these isolated references, numerous reports[103, 485, 486, 639, 1052, 1187, 1188, 1286, 1327, 1947, 2000] established that, next to colchicine, phenylbutazone is probably the most important therapeutic agent available for acute gouty attacks, especially for patients refractory or oversensitive to colchicine. Bartels[103] administered 300 mg. every six hours for 48 hours; if there was then no benefit, further treatment was not desirable. Smyth[1947] gave 100 to 200 mg. every four hours, and reported a striking reduction of joint pain in from eight to 12 hours in the majority of instances. Lockie[1286] employed a combination of 200 to 300 mg. of phenylbutazone a day for two or three days, with suboptimal doses of oral colchicine. [There is increasing evidence that phenylbutazone is a reliable drug in the control of acute joint symptoms in gout. Some of us consider it just as effective as colchicine and generally safe for short-term administration.

The factor of ultimate safety remains for further clinical experience to establish. —Ed.]

Intramuscular phenylbutazone was used[1187, 1188] effectively; absorption of this agent may be retarded[2000] by precipitation at the injection site. Rectal suppositories of phenylbutazone were also employed.[1187, 1188] Although in short-term therapy the undesirable side-effects of this drug were minimized,[1052] they are not unknown, having been reported[1187] in an incidence of 9% in a large experience. This investigator also emphasized that severe side-effects from phenylbutazone usually occur early in treatment. [The type and incidence of toxic reactions to phenylbutazone are discussed under the heading, Treatment of Chronic Gout: Uricosuric Agents.—Ed.]

Steroid Therapy. Recent literature laid less stress upon steroid therapy in acute gouty attacks. Although the efficacy of these agents was generally conceded,[103, 216, 292, 541, 973, 1188, 1367, 1947, 1972, 1986, 2057, 2195, 2196] lack of persuasion of their merit or untoward effects associated with their use were reported by others.[13, 918, 1535, 1738, 2155] Generally there was no need to resort to either hydrocortisone, prednisone, prednisolone or ACTH in acute gouty arthritis, since better and more appropriate agents are available.[918] [We agree. This is not to deny, however, that indications may in unusual instances exist for steroids in management of the acute attack of gout.—Ed.] Favorable reports have appeared[541, 1188, 1947] concerning intravenous ACTH or oral hydrocortisone.[1972] Most observers were in agreement[1947] that cortisone has no place in the treatment of gout, for failures are frequent and some patients are worse with this drug. With respect to oral hydrocortisone and prednisone, "good" results were reported[1188] in less than half of the patients; in the remainder, these agents were poorly tolerated and were associated with a tendency for exacerbation after the initial subsidence of the acute attack. In another instance[541] the effect of prednisone upon acute gout was not particularly favorable in comparison to that of intravenous ACTH. Although time has failed to substantiate entirely the reports suggesting that sharp withdrawal of ACTH may precipitate another attack of gout,[1367] it was agreed that colchicine in reduced doses must[103, 1367, 1947] be given concomitantly with systemic steroid therapy, and that steroid dosage should be gradually decreased over a period of several days. Use of ACTH to precipitate attacks of gout as a diagnostic measure has not proved to be of great value.[1367] It was probable that the improvement in gout associated with ACTH did not result from the incidental effect of increased uric acid excretion;[292] the possibility has been suggested[2155] that ACTH inhibits the chemical synovitis in gout. Adlersberg[13] stressed the possibility of thrombo-embolic complications in gout treated with ACTH or cortisone.

The gouty joint was sometimes favorably affected by local injection of hydrocortisone or the tertiary-butyl ester of hydrocortisone.[103, 216, 1188, 2057, 2195, 2272] All agreed that this form of therapy should be employed as an adjunct to and not as a substitute for standard therapy. It was plain, however, that the response to local steroids was not always favorable, for in some instances[1188, 1972, 2195] they produced temporary increase in pain.

Intercritical Period. It was emphasized[1777] that "success in overcoming acute attacks does not necessarily imply successful control of the underlying disorders; neither should it be assumed that the responsibility of the physician has been discharged when the acute attack has subsided." Institution of successful prophylactic measures against repetition of the acute attacks should "encompass most of the time for all patients with gout."[2057] The program "comprises few drugs and few prohibitions." A high fluid intake aided elimination of uric acid. Weight reduction was emphasized; dietary restrictions as viewed by most writers were otherwise generally minimal. Food substances

high in purines were generally to be avoided; alcohol and red meat were permitted in moderation. [This liberal concept is not accepted by all rheumatologists. Ed.] The amount of physical activity was determined by factors other than the presence of gout. The importance of identifying and eliminating all possible agents which might precipitate attacks of gout was again stressed.

Talbott[2056] regularly administered varying doses of colchicine throughout the year to his patients in the intercritical period. A small number take one to three tablets (0.5 mg. each) per week; for patients moderately afflicted, two to three tablets were taken daily; in exceptional situations, and if tolerated, maintenance colchicine in doses up to one tablet four times a day was recommended. He reported that on this simple and inexpensive régime only a minority of patients lost more than a day or two per year from their work because of acute or chronic distress; a significant number went two, three, four or five years between attacks; less than 5% reported at periodic intervals because of complaints. Particular stress was laid upon the routine use of colchicine one or two days before surgical operations, and the ingestion of added amounts of colchicine in the event of an acute infection.

Rosenberg,[1777] on the contrary, did not employ interval colchicine, for he did not feel that its benefits are as yet adequately demonstrated. [The value of colchicine as interval treatment has not yet been investigated critically.—Ed.] The place of phenylbutazone in the management of the intercritical period has not been well established. At the present stage of our knowledge, continuous or maintenance administration of phenylbutazone, comparable to use of maintenance colchicine, was considered to be unjustified in the patient experiencing two to three attacks of gout a year.[2000] [We agree.—Ed.]

Treatment of Chronic Gouty Arthritis or Tophaceous Gout

From the therapeutic point of view, a distinction between acute and chronic gouty arthritis must be made. In the past therapy has "been almost wholly preoccupied with control of recurrent gouty arthritis; the most imperceptible accumulation of tophaceous deposits appears to have been accepted as inevitable and irremediable save for what could be accomplished by surgical incision or amputation."[855] Colchicine, the sovereign remedy for acute gouty arthritis, when given alone in regular prophylactic doses has failed to prevent the progressive development of chronic gouty arthritis. Furthermore, in this stage the response to colchicine was less dramatic and often incomplete.[1947] Since the essential factor in pathogenesis of chronic gouty arthritis is positive uric acid balance, the essential aim of management was to induce a state of negative uric balance and to maintain this as long as might be required.

Dietary Management. Opinion remained divided as to the importance of dietary control of gouty arthritis.[103, 104, 855, 1188, 1286, 1392, 1747, 1777, 1947, 2057] Conservative approach to the problem conceded[1947] that theoretically the diet of the patient with gout should be low in purine-rich foods, but from the practical standpoint, most patients who have only an occasional attack refuse to adhere to a rigid diet. It was only when recurrences were as frequent as three to four per year that most patients would follow such a dietary schedule. There was no evidence to prove that adherence to a rigid low-purine diet reduced the frequency of acute gouty attacks or prevented the development of chronic gouty arthritis or the complications of the disease. Studies using isotope technics reaffirmed that ingested preformed purines were not the only source of uric acid; they were synthesized in the body from the

simplest derivatives of carbohydrates, fat and protein. Complete control of urate formation by diet regulation was therefore considered to be obviously impossible. On the basis of these facts, patients were advised to avoid foods particularly high in purines, such as liver, sweetbreads, kidney, sardines and anchovies. In addition, moderate restrictions are placed on meats, fish, seafoods, beans, peas and lentils.

More rigid control of diet was advocated by others.[835, 1403, 1777] Gutman [855] emphasized that the degree of reduction in uric acid production effected by dietary restriction can be roughly gauged by the resulting fall in urinary uric acid excretion, usually accompanied by more or less decline in serum urate levels. He prescribed a basal diet with a low purine, poor fat, and restricted protein content (60 to 70 gm.). Serum urate level and urinary uric acid excretion were determined while on the basal diet and at intervals after appropriate alterations in the program. The mean decline in serum urate achieved with the basal diet in 114 gouty subjects averaged 1.1 mg.%. In some instances, it was emphasized, the dietary effect on serum urate proved to be an important factor in management and, indeed, essential even with the maximal uricosuric effect obtainable with probenecid. [Significantly more uric acid is formed in the body on a high protein diet than on a low protein diet, as shown by glycine N^{15} studies. This remains the only known method of controlling *de novo* purine biosynthesis in the human.—Ed.]

A low protein diet was described [203] as an adjunct to alkalinization and hydration in management of patients with recurrent uric acid stones.

Uricosuric Agents. As has been pointed out,[895] a sound theoretic case could be made for starting a uricosuric drug as soon as the diagnosis of gout is firmly established, and for continuing it for the remainder of the patient's life. The point was made that it was impossible to be sure of the point at which the deposits of urate first appear in the tissues and initiate the irreversible changes. Many patients have had years of freedom after a single acute attack of gout. To start lifelong treatment after a single attack of gout demands a singularly firm physician and a particularly amenable patient. [Unless the patient is completely informed concerning the rationale and accepts the philosophy of protracted and expensive therapy, the program will likely be a failure.—Ed.]

Phenylbutazone. Although phenylbutazone has become well recognized as an effective agent in acute gout, its place as a uricosuric agent in the long-term management of chronic tophaceous gout is less well established.[1052, 1187, 1947, 2000, 2057] There has been, in fact, considerable disagreement as to the effect of phenylbutazone upon uric acid metabolism. Studies reported by Johnson [1052] in chronic gouty arthritis revealed detectable amounts of phenylbutazone in the blood and urine with serum levels proportionate to dosage which rose to a peak at four hours. Blood levels obtained after a dose varying between 0.4 and 1.0 gm. varied from 5.8 to 18.7 mg.%. Reduction in serum urate occurred in each of the 16 patients tested, and averaged 3.1 mg. per 100 ml., and in no instance was there increase in urinary uric acid that could account for the drop in serum uric acid. Similar observations relative to the effect of phenylbutazone on serum urate and urinary acid excretion were reported by others.[1187, 2000]

In contrast, Smyth and Huffman [997, 1947] reported studies on eight patients with gout given daily doses of 800 mg. of phenylbutazone. The mean fall in serum urate was 3.8 mg. per 100 ml.; in seven individuals the mean increase in 24-hour urine urate excretion was approximately 50% over the control values. Wyngaarden,[2259] by direct measurement of the rate of uric acid biosynthesis, using N^{15}-labeled uric acid in subjects receiving phenylbutazone, was unable to support the view that phenylbutazone suppressed uric acid formation. [The lowered uric acid may have resulted from dilution by fluid retention resulting from the sodium-retaining property of phenylbutazone.—Ed.] Yü [2275, 2276] and Brodie [266] and associates have clearly shown the uricosuric effect of phenylbutazone to be due to depression of tubular reabsorption

of urate. They further pointed out a sequence of renal effects associated with rising plasma phenylbutazone levels corresponding to various dosages. These observations explained how, without suppression of uric acid biosynthesis, administration of phenylbutazone may cause lowering of the serum uric acid level without uricosuria, indeed in the face of uric acid retention. These studies established that phenylbutazone, like salicylates and probenecid, share the characteristic paradoxic effect of uricosuric agents, whereby large doses increase and small doses suppress renal excretion of uric acid.

The potential toxicity of phenylbutazone no doubt explains the paucity of information existent with respect to its use as a long-term uricosuric agent in chronic tophaceous gout. Some [1367, 1947] were of the opinion that the therapeutic response in gout to phenylbutazone could not be explained by its uricosuric action. Whether this is due to an anti-inflammatory action, is purely analgesic, or is due to some unknown action on uric acid metabolism remains obscure. Others [1187, 2155] emphasized that the effect of phenylbutazone in lowering the serum uric acid in gout may be the most important pharmacologic action of the drug. It was suggested [1187] that delay in degradation of nucleic acid by phenylbutazone may present a key to its fundamental mechanism; its effect was reported upon certain enzyme systems; it inhibits the growth of yeast. Observations have been reported [266] upon the physiologic behavior of a compound in which the butyl side chain of phenylbutazone was replaced by a phenylthioethyl group (G-25671). Like phenylbutazone, this preparation exerted a distinct antirheumatic effect but produced little or no sodium retention; its uricosuric effect appeared to be superior to that of phenylbutazone. The uricosuric action of ethyl biscoumacetate has recently been described.[1968] [Zoxazolamine (Flexin),[1712] a widely used muscle relaxant, has recently been found to have potent uricosuric effects.—Ed.]

Probenecid (Benemid, p-(di-n-propylsulfamil)-benzoic acid). Interest remained high in this important uricosuric agent. The optimism of Bartels [104] was shared by others when he stated that probenecid will "effectively control gout regardless of the severity of the disease and accomplish what insulin has done so brilliantly for diabetes." [Failures with probenecid therapy are not uncommon, and can be attributed to the expense of the preparation and the failure of patients to take a medication for prolonged, symptom-free periods.—Ed.] The claim also appeared reasonable that the development of tophaceous deposits and disabling chronic arthritis was now preventable in most cases of gout.[854] Metabolic studies have been reported by several investigators.[206, 207, 854, 855, 1368, 1916, 2275] In the gouty subject,[854] as in normal man, virtually complete filtration of urate was demonstrated at the glomerulus, with subsequent reabsorption in the proximal tubule convolutions of all but 5 to 10% of the filtered urate. The action of probenecid was stated to be inhibition of tubular reabsorption of urate by an as yet obscure effect on presumably enzymatic transfer mechanisms.[854] This led to increased uric acid excretion associated with increased urate clearance. The action of probenecid was presumably similar to that of salicylates but was five to eight times as potent.[206] The uricosuric action of probenecid appeared to be selective;[854] however, small but significant sodium chloride and water diuresis sometimes was evident. No other important phase of metabolic activity appeared to be influenced by long- or short-term administration of the drug. Probenecid did not induce tubular secretion of urate, although it did inhibit tubular secretion of penicillin, p-amino-salicylate, p-amino-hippurate and phenolsulfonphthalein.[854, 1916] Intrinsic and extrinsic factors which significantly

affected the uricosuric response to probenecid included the processes which determine the rate of urate production and excretion and dietary latitude.[854]

In 58 gouty subjects[854] on a standard restrictive diet and receiving probenecid, the mean urinary urate excretion rose after one to two weeks approximately one third with 0.5 gm. daily doses, and about one-half above the initial level with 1.5 gm. doses. Beyond the 1.5 gm. dosage level, although there were further individual increases in urinary urate excretion, the mean figures declined. In almost half of the cases the concentration of serum urate, and presumably that in the interstitial fluid, was reduced to within the upper limit of normal (6 mg.%). It could not be reduced below 7 mg.% in about 30% of the cases. In those individuals with vigorous overproduction of urates, maintenance of satisfactory serum urate levels with probenecid was difficult and, in occasional cases, impossible even with 3 gm. a day. In three cases in whom renal damage was present it was impossible even with higher dosage levels to maintain satisfactory serum urate levels. Increased urinary urate secretion was demonstrable in the average case, usually within 40 minutes after ingestion of probenecid, and reached the peak within four hours; the fall in serum urate levels was usually evident within 24 hours.[854] Upon discontinuance of probenecid, the uricosuric effect was found to cease within 24 hours and was often followed by urate retention for a day or two; return of the serum urate to the initial level occurred in a few days or a week. Intermittent dosage with probenecid for just a few days in the week was therefore futile. In Bartels' experience[104] the average dose of the drug required to sustain a normal serum urate level was 1.1 gm. Two main factors appeared to be important in restoration of normal values: size of dose and duration of treatment. Occasionally patients required months of therapy on 2 to 3 gm. daily before the level became normal. The fall usually occurred, however, within from three to six weeks. In 88 of 95 cases the serum uric acid was restored to normal (6 mg.%); the average pretreatment value was 7.8 mg.%; the average treatment level was 4.8 mg.%, a 38% fall. Of 42 patients who received probenecid for from 12 to 30 months, the serum uric acid level was restored to normal and maintained there in 38 cases. Others[103, 974] suggested smaller initial dosages of probenecid.

The limiting factor in the duration of uricosuric response to continued administration of probenecid was depletion of mobilizable urate stores in the tissues and circulating fluids.[854] Short- and long-term quantitative studies of urinary urate excretion induced in gouty subjects (as well as in normal controls) by probenecid were reported.[854, 1368] In one study,[1368] in the first five days of probenecid administration the calculated mean loss of uric acid from the plasma was 149 mg., while the mean excess urate appearing in the urine over the same period was 2,135 mg.; these discrepancies became less marked with longer periods of observation. In patients with extensive tophaceous deposits, with probenecid uricosuria continued for longer than three years, the total quantities of excess urate recovered in the urine exceeded 100 gm.[854] These studies gave support to the concept that uric acid in the solid phase (as represented by the tophus) was in equilibrium with that in solution in the tissue fluid. As judged by the prevention or mobilization of tophi, the critical level of serum uric acid for establishment of negative uric acid balance appeared to exceed the upper limits of normal in most cases.

Clinical Response. This was measured in terms of decrease in joint stiffness and pain, decrease in acuity and severity of acute recurrent gouty attacks, improvement in the sense of well-being and decreased size of tophi. Depletion of the tissues of uric acid appeared to contribute[854, 855] to a decrease in severity and frequency of acute attacks of gout. Improvement was reported in joint stiffness and slow disappearance of joint pain in 17 (94%) of 18 cases receiving

probenecid for from eight months to four years. In every case, recurrent acute gout attacks were reduced in severity and frequency. Bartels[104] reported satisfactory results in 39 of 42 patients receiving probenecid (for from 12 to 30 months): 15 (36%) suffered no further attacks of gout; 24 suffered from attacks of gout during the first six to nine months of treatment, but these were usually minor, and ultimately there was freedom from attacks. Three of 42 patients were considered to have an unsatisfactory response to probenecid in spite of normal serum urate levels; one patient continued to have severe attacks for 12 months; the attacks were in no way different from those before treatment was started.

In Gutman's[854, 855] 43 patients who received the drug for from eight months to four years, in addition to healing of sinuses, tophaceous deposits were reduced in size in 24 (56%). In no instance, he said, did tophi demonstrably increase in size or new tophi appear. In eight cases, premature and usually unauthorized discontinuance of probenecid was followed by appearance of new tophi within several months. Although tophi were observed to stop discharging and to decrease slightly in size,[207, 1188] there were no retrogressive x-ray changes.[104] [This same author[105] and others have reported radiologic evidence of reconstitution of bone and joint structures after prolonged use of probenecid. —Ed.]

The potential ability of probenecid to "desalt" the kidney, with concomitant improvement in renal function, was a subject of great interest and importance. "Reversal" of renal insufficiency by probenecid (based on improvement in phenolsulfonphthalein excretion, some improvement in concentrating ability, and clearing of urinary sediment) has been reported[1627] in a patient with tophaceous gout in a period of approximately three years. [Most investigators have had less success with probenecid in achieving a favorable effect on serum urate level as well as in improving renal function when the latter is severely impaired.—Ed.] The problem of renal colic or passage of uric acid gravel was discussed. Some[108, 206, 1286, 2057] reported little or no difficulty, even when probenecid was administered to patients with known renal calculi; urinary frequency was observed. By contrast, Gutman[854] reported that 15 of 41 side reactions from probenecid observed in 120 gouty subjects were in the nature of renal colic or passage of gravel; there were five cases of renal colic. All were agreed upon the wisdom of a large fluid intake and, in some instances, alkalinizing agents to attempt to avoid these complications. In a review[206] involving 2,502 patients receiving probenecid, side-effects were observed in 175; 35 of these were related to the urinary tract. Otherwise, the most common manifestation was of gastrointestinal origin, occurring in 3.1%; skin rashes were observed in 34 patients; typical hypersensitivity reactions occurred in eight individuals. Most investigators agreed that the toxicity of probenecid is clinically unimportant; to date[206] there have been no deaths attributable to probenecid therapy in over 2,500 patients. [One death from fatal massive necrosis of the liver attributed to hypersensitivity to probenecid has recently been reported.[1728] Successful desensitization to probenecid has been described[73] using minute daily oral doses and progressively increasing the dose until therapeutic levels were achieved.—Ed.]

There was said to be reasonable presumption that probenecid, by reason of its profound uricosuric action, may in some cases act as a chemical stress upon the biochemical equilibrium of the gouty patient and precipitate an acute attack of gout.[206] The incidence of this phenomenon in experienced hands ranged from 57%[104] in the first six to nine months of therapy to about 9%[206, 854] in the first few days of therapy with probenecid. Most investigators follow the precaution of administering small

maintenance doses of cholchicine with initiation of probenecid therapy; later, colchicine may be discontinued. Others [1188, 1947] find that phenylbutazone, in this difficult period, may be a useful agent.

Variable indications for probenecid therapy and the manner in which it should be administered were offered.[103, 206, 396, 854, 855, 1188, 1286, 1367, 2057] [In our opinion, the indications for uricosuric agents in gout can be listed as follows: (1) the demonstration or development of visible tophi, including those noted by x-ray; (2) patients in whom the frequency and severity of gouty attacks is increasing in spite of maintenance colchicine; (3) chronic gouty arthritis in which muscle and joint stiffness and aching are not controllable by ordinary means; (4) documented increase in serum urate to appreciable levels above 8 mg.%.—Ed.] Talbott [2057] used probenecid in doses of 0.5 gm. or 1.0 gm. daily in patients mildly afflicted. Usually, however, prophylactic colchicine was quite adequate in these instances. Patients who were or had become moderately afflicted were advised to take 0.5 to 1.0 gm. of probenecid daily; those severely afflicted, from 1.0 to 2.0 gm. daily. With respect to dosage and duration of treatment, those mildly afflicted he allowed considerable freedom, in contrast to those severely afflicted, who were advised to remain on probenecid and colchicine for an indefinite period. Bartels [103] also utilized probenecid in mild cases to control serum urate levels and prevent the deleterious effect of prolonged hyperuricemia. If a preliminary trial of salicylates failed to restore the serum urate to normal, probenecid was substituted for the aspirin; colchicine was discontinued when the serum uric acid fell to normal. Patients with tophaceous gout must accept the fact that the medication must be taken daily and continued for many years. Boger [206] stated that 2 gm. of probenecid per day represent the average dose tolerated over a prolonged period; if renal function was impaired, this dose was considered to be excessive.

Probenecid was used in combination with bacitracin; [759, 1423] the possible ill effect of this combination was discussed.[759] A method has been described [2097] for determination of probenecid in body fluids. The mechanism of increased renal excretion of urates during administration of probenecid has been studied.[456, 459, 1654] Studies have been reported [1982] of the effect of probenecid upon phosphate excretion and other metabolic processes. The influence of probenecid upon urinary excretion of phosphate in hypoparathyroidism has been investigated.[1584]

Salicylates as Uricosuric Agents. An excellent summary of the history of salicylates in gout appeared,[1041] and interest [1041, 1356, 1355, 1367, 1368] in the uricosuric effect of this agent in chronic tophaceous gout was reviewed. Until recently, the immediate depressing effect of salicylates on serum urate was generally believed to be short-lived. Marson [1355, 1356] has presented convincing proof, however, that continuous administration (18 to 60 months) of sodium salicylate controls serum uric acid levels in gouty patients; this was associated with relief of symptomatology, mobilization of urate deposits, as shown by shrinkage or total disappearance of tophi, recalcification of areas of bone absorption, and a prolonged increase in urinary uric acid levels. Sodium salicylate was administered in a daily dosage of 60 to 120 gr. (usually 90 gr.), normally equally spaced in three doses. Marson found after the first few weeks that the large majority of patients tolerate this dosage with either complete freedom from salicylism or occasional and mild tinnitus and deafness; in only five of 40

patients were toxic symptoms sufficiently severe to prevent adequate continuous therapy. In 17 patients receiving salicylates, the uric acid was maintained at a mean of 50% of the initial level, and in 13, below the normal mean level. This investigator's data suggested that salicylates have an appreciably greater depressant effect on serum urate than does probenecid. [This point is disputed: others [207] claim that the uricosuric effect of probenecid is more potent than that of salicylates.—Ed.] As long as chronic symptoms exist, the serum urate levels should be maintained at the lowest possible level. One investigator [1355, 1356] suggested that if facilities for close study were not available, it was probably more satisfactory to commence treatment with probenecid. In the event the patient does not get full relief in six months he should not be regarded as incurable, but salicylates should be given a trial. Intermittent salicylate therapy (80 gr. daily, four days on and three days of rest) was preferred by others [1041] because of improved tolerance and limited toxicity. Two American investigators, Bartels [103] and Hoffman,[974] have recently discussed salicylates as uricosuric agents; both employed high doses of aspirin (2.3 to 1.3 gm., three to four times a day) for five or three successive days of each week; if this plan failed to restore the serum uric acid to normal, probenecid was substituted. McEwen,[1403] while concurring that salicylates in doses of over 5 gm. daily are often effective uricosuric agents, stressed that toxicity was an important factor.

Salicylates shared with other uricosuric agents the characteristic paradoxic effect whereby uric acid clearance is increased at high plasma drug concentrations but depressed at low plasma drug concentrations.[2275] Interesting debate continued as to the effect of coincident administration of salicylates and probenecid. Several investigators [205, 207, 854, 1585] claimed that the administration of acetylsalicylic acid and sodium salicylates completely nullifies the effect of probenecid. In one representative study [1585] it was observed that the inhibitory effect of salicylate began to occur at sustained plasma salicylate levels between 5 and 10 mg.%. The administration of salicylates during probenecid therapy annulled the lowering of serum urate induced by probenecid; similarly, probenecid annulled the lowering of serum urate caused by salicylate medication. Contrary evidence has been published by Marson [1356] to the effect that coincidental administration of these two agents did not nullify their uricosuric effect. In unpublished studies this investigator [974] has stated that salicylate levels achieved with single doses of aspirin are not likely to interfere with the uricosuric effect of probenecid. [Since uricosuria is not augmented by concurrent administration of these two agents, little reason appears to exist for their simultaneous use in large amounts in gout.—Ed.] Curiously,[205] when acetylsalicylic acid was administered orally in appreciable doses with probenecid, the former did not interfere with the enhancement effect of probenecid upon penicillinemia.

Prolonged Administration of Steroids in Chronic Tophaceous Gout. Most agreed that there was little place in tophaceous gout for continuous administration of steroid agents except, uncommonly,[918] in the presence of exacerbations uncontrolled by other measures. When prolonged maintenance therapy with cortisone, hydrocortisone or prednisone was attempted,[1188] patients almost invariably became worse. An interesting case was reported [35] of suppression of acute arthritis and mobilization of solid, presumably urate deposits in a gouty patient by prolonged administration of cortisone (50 mg. a day for 22 months). A case was reported [2243] of tophaceous gout distinguished by the continuous administration of ACTH in suppressive doses for four years.

Surgical Measures in Chronic Gouty Arthritis. The skilful use of potent uricosuric agents will very likely reduce the necessity in the future for surgical measures in tophaceous gout. In one remarkable series [854] of 43 patients with tophaceous gout treated with probenecid for from eight months to four years, surgical drainage or amputation was not required; discharging sinuses healed in two of three cases. It was concluded: "Surgical intervention should be limited to removal of easily accessible and discretely circumscribed urate deposits, particularly involving the olecranon and prepatellar bursae since these are apt to be insulated and refractory to medical management unless treatment is instituted early in their development." Reduction in the frequency of attacks of gouty arthritis by the removal of large tophi was mentioned.[1286] All were agreed that the possibility of postoperative gout necessitates preoperative and postoperative medication with colchicine.

Studies on Colchicum. In an impressive discussion [925] of the history and properties of *Colchicum,* it was stressed that the inhibitory effect upon completion of mitosis of cells was the most important known action of the herb. This is induced by 0.001 of the amount necessary to produce other observable metabolic effects; the action, moreover, was remarkably selective. This may or may not be related to the favorable effect of colchicine in acute gout. Hormonal, enzymic, or shocklike effects and reduction of vitamin C content of tissue have been postulated as related to the effect of the drug. Colchicine was moderately bacteriostatic and had no effect on uric acid excretion. [Its effect or lack of effect on uric acid metabolism awaits elucidation.—Ed.] Two distinct actions appeared to be involved in the poisonous effects of colchicine. First was the immediate irritating effect on the gastrointestinal tract, possibly due to excitation of the nerve endings of smooth muscles, but more likely through a central effect. The lethal effect of the drug, which is delayed even in relatively enormous doses, was thought to be caused by vasomotor and respiratory paralysis. The beneficial effects of colchicine on malignant growths were first observed by Amoroso in 1935 in patients treated primarily to relieve acute attacks of gouty arthritis. The effective doses unfortunately are only just below the lethal dose. Interesting and undoubtedly profitable suggestions for future investigations with colchicine were made by this author.

Correlation of clinical improvement after colchicine, with restoration of sedimentation rate and plasma fibrinogen to normal, was described.[1117] The eosinopenia produced in the normal rat by colchicine was partially suppressed after hypophysectomy in that animal.[1494] The simultaneous administration of three agents, widely different in chemical structure (meso-inositol, adenosine-triphosphate and tropolene), was shown [143] to counteract the effect of colchicine on the mammalian fibroblast. The possibility existed that colchicine may act to produce metaphase arrest by functioning as an antimetabolite in the chain of reactions required for nuclear divisions. Striking alteration in mast cell morphology was induced [1578] by colchicine and other [1103] cytotoxic agents. A favorable clinical study [1634] was reported of the treatment of chronic myeloid leukemia with a *Colchicum* derivative (Colcemide).

Studies on Cinchophen. There was very little new information concerning cinchophen. In especially severe or stubborn episodes of gout which resist the usual trials with colchicine, Rosenberg [1777] described the use of cinchophen (0.5 gm. three times daily). He pointed out that hepatitis following administration of cinchophen for treatment of gout had not been reported. A case of agranulocytosis associated with cinchophen administration was reported.[1476] Studies [923] on detoxication mechanisms included a report of the effect of cinchophen on glucuronide synthesis by the liver. In an investigation of the production of cinchophen ulcers in dogs, estrogens

were observed[922] to prevent the inevitable reduction in duodenal secretion induced by cinchophen.

Treatment of acute and chronic gout with a cinchonic acid derivative (3-hydroxy-2-phenylcinchoninic acid, or H.P.C.) was described;[1782] treatment for about one month was required before appreciable improvement was observed. The frequent occurrence of skin lesions made maintenance therapy impractical.

The Uric Acid Problem

Biosynthesis of Purines. The identification of the ultimate precursors of purines as such simple materials as glycine, formic acid, carbon dioxide and ammonia has been summarized in previous reviews.[1] Remarkable progress in the understanding of the mechanisms of purine biosynthesis has resulted from intensive studies.[833] While the details of the biochemical studies are beyond the scope of this review, the present concept of purine biosynthesis and of the role played by folic acid derivatives can be summarized. On the basis of reported information, it was evident that purine rings are synthesized as their ribotide derivatives, rather than as a free base. This present concept involved the early interaction of a ribose phosphate derivative with glutamine and glycine to form an aliphatic ribotide having the general structure of glycine-N-amido-5′-phosphoribotide. At this point a formyl derivative was introduced to form the 8-C of the purine, and, following a number of reactions, 5-amino-4-imidazolecarboxamide ribotide was formed. This in turn reacted with a formyl derivative which was introduced in the 2-C position to yield inosinic acid. A folic acid derivative, apparently a reaction product between citrovorum factor and ATP, was identified as catalyzing the over-all reaction by which the formyl group is introduced into the 2-C position to close the purine ring. A folic acid derivative also appeared to play a role in the introduction of the 8-C as well as the 2-C position.[833]

It was shown that the methyl group of methionine can serve as a source of the formic acid which was introduced eventually into carbons 2 and 8 of the purine ring.[1910] [Previously it had been shown that the carbon of formic acid, lactate, serine and threonine may be incorporated in these positions, presumably through the intermediate step of the formation of "active 1-carbon compound."—Ed.]

There was further interest in the study of oxypurines in the blood and urine. The enzymatic method suggested by Kalckar, combined with spectrophotometric determinations, was applied to human plasma and urine,[1069] and permitted differentiation of hypoxanthine and xanthine.[1070] In freshly drawn human blood the plasma concentration of hypoxanthine plus xanthine was 1 to 3 μg per milliliter. There was a hundredfold increase in this concentration after the blood had stood for 24 hours, due to the red blood cells giving off hypoxanthine and xanthine.[1068] Plasma glutamine and oxypurine levels were studied in 10 normal subjects and 10 gouty subjects. No differences were observed in the plasma glutamine content between the two groups. A plasma oxypurine level was clearly elevated in only one gouty subject. This study failed to confirm a previous report of abnormally low levels of glutamine and high levels of oxypurine in the blood of patients with gout.[1857]

An additional case of the rare condition of xanthinuria was reported. Xanthine was identified in the urinary calculus and by isolating it in pure form from the urine. The patient, a four and one-half year old girl, excreted large quantities of xanthine and only traces, if any, of uric acid. The blood uric acid level was very low.[502] A

method employing ion exchange separation and paper chromatography permitted investigation of individual variations in urinary excretion of purines on a qualitative and semiquantitative basis. Two normal subjects on a purine-free diet excreted a total of more than 30 mg. per day of nonuric acid purine derivatives. Those identified, in order of diminishing abundance, were hypoxanthine, xanthine, 7-methylguanine, adenine, 1-methylguanine and guanine.[2197]

Isotopic Tracer Studies. The knowledge of uric acid metabolism derived from tracer studies (which have been summarized in previous reviews) was discussed in relationship to gout.[973, 2009, 2059] Of particular interest was the demonstration that a substance which had been identified by biochemical studies as an intermediate in the biosynthesis of purines was rapidly incorporated in large amounts into the uric acid of humans. 4-amino-5-imidazolecarboxamide (AIC) was synthesized with a C^{13} label in the 4-C position and fed to two normal adult males at a dosage level of 14 mg. per kilogram. Approximately 20% of the AIC fed was recovered unchanged, with its isotope undiluted, from the urine excreted in the first eight hours. Between 20 and 23% of the C^{13} was recovered in the uric acid excreted in the two to three weeks following ingestion of the material. The isotope concentration in the uric acid was maximal at about 14 hours and declined rapidly thereafter. The data indicated the existence of a mechanism in man for the prompt conversion of this precursor to uric acid, and suggested the existence of a second, less direct mechanism whereby carbon from this material enters uric acid, possibly by way of body purines. Results obtained when both labeled AIC and labeled glycine were administered together indicated that AIC administration interfered with the synthesis of uric acid from glycine.[1853] Yeast nucleic acid labeled with N^{15} in both the purine and the pyrimidine moieties was fed to two normal and one gouty subject. The slopes of curves for the excretion of isotopic urinary uric acid were very similar to the uric acid "turnover rates," which were determined separately after the intravenous injection of isotopic uric acid. Normal and gouty subjects did not seem to differ significantly in their ability to do this.[2232] Studies in two nongouty and two gouty subjects following the subcutaneous administration of formate labeled with C^{14} indicated that this precursor was utilized for uric acid synthesis more rapidly and to a greater degree in the gouty subjects.[1976] [These studies are in accord with the findings in *some* gouty patients in whom the rate of urate synthesis has been determined with N^{15}-labeled glycine.—Ed.]

The possibility that uric acid may be destroyed in the human body has been reopened by isotope studies, in which a discrepancy has been observed between turnover rate and excretion of uric acid.[1] Uricolysis, as evidenced by a decrease in the uric acid content of whole blood as well as of plasma, was demonstrated on incubation with white blood cells or red blood cells. It was thought conceivable that a diminished rate of uricolysis in gouty patients could contribute to the hyperuricemia, as the mean percentage decrease was somewhat less in gouty subjects as compared to normal. This difference persisted when the plasma of normal subjects was raised to a hyperuricemic level by addition of urates.[168] The conversion of uric acid to allantoin in the human was investigated by injecting N^{15}-labeled uric acid intravenously, and the determination of allantoin was measured by the use of an isotope dilution technic. In one normal and one gouty subject there was no significant conversion of the injected N^{15} uric acid to urinary allantoin.[811] [Uricase, the enzyme

responsible for the conversion of uric acid to allantoin in lower animals, has never been demonstrated in human tissues.—Ed.]

Preliminary studies suggested that the degree of incorporation of isotopic glycine into uric acid was not affected by folic acid administration in one normal and two gouty subjects.[180] Similar conclusions were drawn from a study of a single subject with gout in whom the administration of large doses of folic acid did not affect the uric acid metabolism as reflected by the level of urinary uric acid excretion.[2299] In a single patient, intensive long-term vitamin E therapy was followed by a reversion to normal of the accelerated rate of incorporation of isotopic glycine into urinary uric acid.[180]

Methods of Uric Acid Determination. Further studies continued to emphasize the shortcomings of colorimetric methods for determination of uric acid, particularly when applied to urine. The direct determination of uric acid in biologic fluids by measurement of its absorption in the ultraviolet range at 2930 Å was applied by several workers. Most workers combined this with the use of the enzyme uricase, measuring the decrease in optical density after action of the enzyme to obtain specificity.[661, 789, 1300, 1656] One method selectively precipitated uric acid as its mercuric salt, redissolved it in sodium chloride, and measured the optical density in the ultraviolet.[152] Further progress in obtaining highly purified uricase was reported.[1334] Another modification of a colorimetric method for determining uric acid in serum was published.[335]

Results obtained by the combination of enzymatic spectrophotometry were compared with colorimetric methods. Lous and Sylvest[1300] found no correlation between the results of the specific enzymatic method and the less specific colorimetric method of Folin and the titrimetric method of Bröchner-Mortensen. Feichtmeir and Wrenn[661] found predominantly high results by the colorimetric method of Kern and Stransky, as compared to the spectrophotometric method using uricase in 190 serum samples. In comparisons of the methods for the determination of uric acid in urine, the colorimetric analysis nearly always gave considerably higher values.[661] The spectrophotometric method using uricase gave the following values for normal men and women in serum: In 143 men, the average concentration was 5.04 mg.%, with 97% of the observations falling within the range of 2.6 to 7.5 mg.%. In 157 women, the average concentration was 3.84 mg.%, with 97% of the observations falling between 2.0 and 5.7 mg.%.[789] In another series, using essentially the same method, 38 males had serum uric acid of 5.89 mg.%, with a standard deviation of 0.86; 40 females had a mean value of 3.75 mg.%, with a standard deviation of 1.11.[661] With this method the 24-hour excretion of endogenous uric acid in newborn infants was found to be about four times the level of excretion in adults; the average concentration of uric acid in the blood from the umbilical cord was 6.1 mg.%, and in the amniotic fluid, 7.2 mg.%.[1656]

Of interest was the demonstration of an elevation of the uric acid content of hair and nails of gouty patients as compared with normal subjects. Normal values ranged from 4 to 9 mg.% of uric acid per 100 gm. of hair or nail parings, and results were above normal in all but one of the 17 gouty patients, the highest values being 26 to 28 mg.% per 100 gm. In 16 cases of serious renal impairment the values were elevated only in the terminal stage of chronic renal disease, but not in the long-lasting mild disease.[223]

Uric Acid Metabolism in Humans. The fate of uric acid in normal and gouty human beings was inferred from the results of studies on the recovery of N^{15} following the intravenous injection of relatively small doses of uric acid labeled with this isotope. In a normal subject the recovery as urinary uric acid was 72 to 78%,

and as fecal nitrogen was 16 to 19%. Less than 4% was recovered as urinary urea and ammonia. When N^{15} uric acid was injected into a normal subject after cholecystectomy, the isotope was found in the bile collected from a T-tube in the common duct. [Unfortunately, conditions did not permit quantitative collection of bile, so that the magnitude of excretion of uric acid in the bile could not be determined.—Ed.] The recovery of intravenously injected N^{15} uric acid as urinary uric acid in six gouty patients was less than in the normal subject (34 to 54%). In three of these subjects the recovery of N^{15} in fecal nitrogen was determined, and was somewhat above normal (25 to 38%). Whether this inability to recover nearly completely the injected dose of uric acid in these two fractions in the gouty subject was due to an artifact of the experimental conditions or to a novel feature of the metabolism could not be determined.[312]

Interest continued to center on the mechanism of renal excretion of uric acid, particularly as influenced by various uricosuric agents. It was demonstrated that the administration of 2 gm. of sodium salicylate to four normal persons increased the excretion of uric acid without changing the glomerular filtration rate; the presumed mechanism of action was therefore a lowered tubular reabsorption. In an experiment in which maximal salicylic acid effect on the kidneys was intended, the uric acid clearance rose to 40 ml. per minute, about one third of the creatinine clearance.[458] It was demonstrated that the effect of salicylate on excretion of uric acid sets in rapidly, and that the excretion may be more than doubled after the administration of a moderate single dose. After the administration of small doses, there was a transient rise in the plasma concentration which could not be explained on the basis of retention of uric acid through inhibition of renal excretion. Presumably a mobilization of uric acid or an increased production from a "precursor" was responsible. After the administration of higher doses of salicylates (3.0 and 4.5 gm. per day), the immediate effect was compatible with the idea of a purely renal depletion of uric acid from the organism, but later the levels of uric acid in the urine and plasma suggested the possibility of increased uric acid production.[457]

Further studies indicated that the primary effect of phenylbutazone in lowering the serum uric acid was accomplished by enhancement of urinary urate excretion. This conclusion was supported by studies using N^{15}-labeled uric acid in two normal subjects during control periods and again during phenylbutazone ingestion.[2259] Mason studied four gouty patients and one normal subject during the administration of 600 mg. of phenylbutazone daily and found evidence of a consistent though mild uricosuric effect, sufficient to account for the observed fall in circulating urate levels. He called attention to the neutralization of this uricosuric effect by the considerable water retention which may occur at the same time, and suggested that this may account for the variable findings in some studies.[1366] Neither phenylbutazone nor probenecid caused a statistically significant uricosuria in two patients without hyperuricemia, although these drugs decreased the pool size of uric acid, increased the turnover rate and decreased the serum urate level. In four patients with elevated serum urate concentrations, the drugs caused statistically significant uricosuria but variable effects on pool size, turnover rates and serum urate concentration. Usually the uricosuric effect of probenecid was statistically greater than that of phenylbutazone. These studies, based on experimental periods of from one to two weeks for each régime, led to the postulation that the uricosuric drugs will produce statistically significant uricosuria only in those patients in whom increased body stores of uric acid are present.[179] However, the same workers subsequently found a definite increase in urinary uric acid output on the first day of probenecid administration to two normal individuals. The amount of uric acid excreted on the second day of administration of the drug was greater than normal but not so great as on the first day. It was therefore suggested that these drugs induce uricosuria in all cases, but that

this increase in the urinary urate excretion is self-limited in subjects with no excess of body stores or urate, since equilibrium between urate production and disposal must be reëstablished.[178]

Further studies probed the interesting finding that when probenecid and salicylates were administered concomitantly, the uricosuric effect of each agent is negated. Acetylsalicylic acid did not interfere with the effect of probenecid in enhancing the blood levels of penicillin during penicillin administration. Salicylates administered alone had no effect in enhancing penicillin blood levels. The lack of interference of salicylate with probenecid in this respect was observed at circulating plasma concentrations of salicylates approximating 10 mg.%, and probenecid concentrations of 5 to 6%. Probenecid plasma concentrations that were pharmacologically active with respect to penicillin had no effect upon the blood salicylate levels.[205] Others studied the effect of probenecid on salicylate clearance in the urine and found that it caused a mean decline of 33% and 40% in the "total" and "free" salicylate/inulin clearance ratios, respectively.[857] [For additional comments on the antagonistic effect of salicylates, attention is directed to the Section on Gout and Gouty Arthritis.—Ed.] The excretory and plasma levels of oxypurines (hypoxanthine and xanthine) remained unchanged after administration of probenecid, cinchophen and colchicine, and none of these drugs influenced the glomerular filtration rate.[788] An anticoagulant drug, ethylbiscoumacetate, was shown to have strong uricosuric effects by impairing urate reabsorption by the renal tubules.[1968] [Zoxazolamine (Flexin) has also recently been shown to be a potent uricosuric agent.[1723]—Ed.]

An abnormality in the uric acid metabolism in hepatolenticular degeneration (Wilson's disease) seems to have been quite clearly identified. Bishop, Zimdahl and Talbott reported two patients with unusually low serum urate values. With the use of isotopic methods, the pool size of both subjects was found to be well below normal, and the turnover rate was approximately twice the normal value. The administration of probenecid accentuated these findings in one subject, but was not tried in the other because of its adverse clinical effects. It was suggested, but not clearly proved, that in this disease the kidney tubule may be inhibited insofar as the reabsorption of uric acid is concerned.[181] These findings were confirmed by subsequent workers, who reported the mean serum urate value in 16 patients with Wilson's disease to be 1.8 mg.%, with a range of from 0.8 to 4.2 mg.%. [These determinations were made by the enzymatic spectrophotometric method.—Ed.] In these subjects the amount of uric acid excreted in the urine was increased, and, following the intravenous injection of uric acid, these patients excreted uric acid in the urine more rapidly than did normal subjects. The data suggested that the alterations in uric acid metabolism in Wilson's disease are due to an inability of the renal tubules to reabsorb uric acid efficiently, and, together with the amino-aciduria and glycosuria seen in patients with this disease, offered additional evidence as to the presence of a renal defect. No correlation was observed between the excretion of copper and that of uric acid, indicating that chelation of copper with uric acid to any appreciable degree was improbable.[1335] Attention was again called to the high level of excretion of uric acid in patients with leukemia, and the danger of uric acid calculus formation in such patients. This danger is particularly likely to be present during treatment with nitrogen mustard or related compounds.[1398]

Uric Acid Metabolism in Animals. Some evidence was obtained indicating that, under certain conditions, uric acid excretion may not be a simple matter of glomerular filtration and tubular reabsorption. Poulsen and Praetorius demonstrated in rabbits that the uric acid clearance at normal plasma levels ranges from 10 to 75% of the glomerular filtration rate. However, if the plasma uric acid concentration was raised approximately fivefold by the intravenous injection of urate, the uric acid was cleared at a rate that may greatly exceed the glomerular filtration rate. These

findings can be explained only on the assumption that a tubular excretion of uric acid takes place at the raised plasma uric acid concentrations.[1655] [These workers have previously reported observations in one man with a very low plasma urate level in whom the urate clearance exceeded the glomerular filtration rate.—Ed.] In vitro work with labeled uric acid served further to identify the oxidation products of uric acid allantoin, and suggested a possible mechanism for these transformations.[476] The intermediate and end-products of the action of uricase and uric acid varied with the pH of the buffer system. In addition to allantoin, urea and alloxinic acid were end-products. The formation of an "allantoin precursor," an unidentified unstable intermediate, was suggested.[332, 333] The oxidation of uric acid by peroxidases was found to carry oxidation beyond the allantoin stage, and a variety of end-products were identified with different systems.[331]

[Such studies are of interest as they indicate possible uricolytic systems in organisms, such as the human, which are lacking in uricase.—Ed.]

CASE REPORTS

IDIOPATHIC HYPOPARATHYROIDISM: REPORT OF A CASE*

By Richard W. Naef, M.D., *Philadelphia, Pennsylvania,* and
Emir H. Adle, M.D., *Teheran, Iran*

Introduction

Idiopathic hypoparathyroidism is a relatively rare disease. In 1952 Steinberg and Waldron [1] collected 51 cases from the literature and added one of their own. They further reported that, out of 213,025 patients admitted to Queen's Hospital over a period of 15 years (1935–1950), only one was diagnosed as idiopathic hypoparathyroidism. Wise and Hart [2] (1952) found only three such cases in a 10-year survey at the King's County Hospital, where the yearly admission rate is 62,000.

Recent reviews of the clinical features of idiopathic hypoparathyroidism are found in the papers of Grant [3] (1953), Sugar [4] (1953), de Mowbray [5] (1953) and Robinson et al.[6] (1954). A case recently studied and treated at Jefferson Medical College Hospital is reported in this paper because the patient presented some unusual features, characterized by exceptionally long duration and advanced severity of symptoms prior to diagnosis, followed by a remarkable recovery.

Case Report

A 30 year old white woman was admitted to the Neurological Service, Jefferson Medical College Hospital, Philadelphia, on March 25, 1957, with the chief complaint of painful muscle spasms. The history was obtained from the patient's mother and husband on admission, and later verified by the patient after her condition improved.

At 14 years of age she had begun to lose some of the hair of her scalp at fairly regular yearly intervals. During the four years prior to admission her hair had been very thin, without regrowth. She had had one generalized convulsion, unrelated to other illness, at the age of five months, and at the age of 22 years she had had a "spell" during which she fell to the floor, stretched out, became rigid and vomited. The episode lasted 10 minutes and was associated with excessive sweating. During a two-year period beginning at the age of 26 (four years prior to admission), she had had several generalized convulsions with urinary incontinence, but other details concerning these seizures were not known.

During the last four years she had had frequently recurring, transient, painful cramps and spasms of the muscles of all extremities, neck and back. There was no loss of consciousness during these episodes, but the patient was unable to speak, respond to commands or make voluntary movements. She was reported to have

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From the Department of Neurology, Department of Medicine and Division of Endocrine and Cancer Research, Jefferson Medical College and Hospital.
Requests for reprints should be addressed to Richard W. Naef, M.D., Department of Neurology, The Jefferson Medical College of Philadelphia, 1025 Walnut Street, Philadelphia 7, Pennsylvania.

screamed or groaned as if suffering great pain, while her arms and hands were tightly drawn up and her legs were either forcefully extended or flexed involuntarily. There were slow twisting movements and arching of her body during these episodes, which varied in intensity and duration; the frequency varied from several attacks on one day, often repeated on several successive days, to one attack weekly.

During the last three years she had been unable to carry out her duties as a mother and had been mostly confined to bed. She had had impairment of memory and inability to concentrate or think clearly for about three years. She had been unable to walk for a year because of unsteadiness and spastic torsion movements of her trunk and limbs. She had difficulty in pronouncing words, and at times her speech was unintelligible. She lost all interest in social activities and events taking place in her home. She was unable to care for her personal habits of cleanliness. Her appetite had been extremely poor for over a year and was associated with considerable loss of weight.

She was delivered at term with the use of forceps, without complications. Her growth and development were normal. She had had no significant diseases other than the usual childhood illnesses. During adolescence and early adulthood she lost all her teeth as a result of gum infections and tooth decay. She had had some loss of hearing on the left side since early childhood. She had had two uneventful pregnancies, seven and five years prior to admission. Menarche had occurred at the age of 14, and the menses had always been regular. During the last four years her muscle pain had increased during each menstrual period.

The patient's father suffered from diabetes, but there were no other significant diseases in her family. Her social history revealed that she had progressed with difficulty but without failure through high school, and had subsequently worked as a machine operator in a dress factory. Her intellectual interests consisted of card playing and reading simply written religious material or comic books. She did not smoke or drink alcoholic beverages.

Physical examination on admission revealed pronounced generalized wasting of subcutaneous tissue and muscles, a weight of 86 pounds, considerable thinning of the hair of the scalp, and dark, periocular pigmentation. The blood pressure was 110/68 mm. of Hg; pulse rate, 80/minute. Neurologic examination revealed the following abnormal findings: There were impairment of comprehension, inability to attend to the interview, delayed and incomplete responses to commands, disorientation as to time and place, and intellectual deterioration. Her speech was dysarthric and unintelligible during tetanic episodes. There were incomplete lens opacities, denser on the left, where the fundus could not be visualized. The right fundus was normal. Vision appeared to be intact, but visual acuity and fields could not be reliably tested. Hearing was grossly intact, but the results of tuning fork tests were unreliable. Her station and gait were characterized by unsteadiness and hypertonicity of muscles, generally with twisting movements of the limbs and trunk. Motor power was good in all extremities, but there were increased tone and dyskinetic incoördination of all movements. The deep tendon reflexes were generally diminished. Pain, temperature and touch sensations were intact, but vibration and position senses could not be evaluated. Chvostek's and Trousseau's signs were positive.

The hemoglobin was 12.3 gm.%, the hematocrit value 37%, and the white blood cell count 5,500 per cubic millimeter, of which 55% were neutrophils, 36% lymphocytes and 8% eosinophils. The urine contained a faint trace of protein and many epithelial cells. Sulkowitch's test was negative. There was 35% excretion of phenolsulfonphthalein in 30 minutes. The Veneral Disease Research Laboratories' and Kolmer's tests were negative. The cerebrospinal fluid was under a pressure of 120 mm. water and contained less than 1 cell per cubic millimeter, 15 mg.% protein, 68 mg.% glucose and 112 mEq./L. chlorides. The cerebrospinal fluid com-

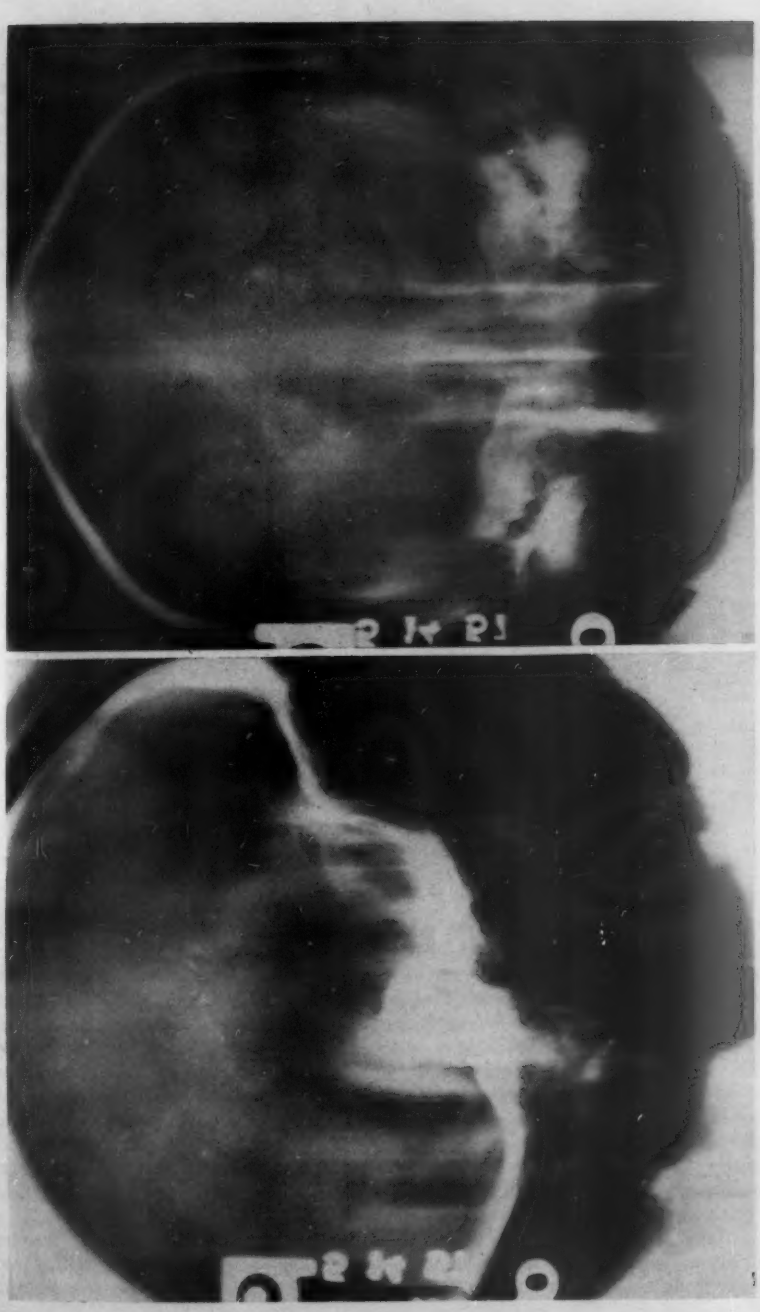

FIG. 1. Laminagram showing intracerebral calcification bilaterally in the basal ganglia.

plement fixation test was negative, and the colloidal gold curve was 0^{10}. Roentgenograms of the chest yielded normal findings. Roentgenograms of the skull revealed fine intracranial calcifications symmetrically placed on either side of the midline in the region of the basal ganglia (figure 1). Roentgenograms of the entire spine, pelvis and long bones revealed numerous growth arrest lines and increased density of the vertebral centra. Initially the serum calcium was 4.4 mg.%, the inorganic phosphorus 7.4 mg.%, and the alkaline phosphatase 0.1 Bodansky unit. The fasting blood sugar was 103 mg.%; serum potassium, 5.0 mEq./L.; serum sodium, 137 mEq./L.; serum chlorides, 94.6 mEq./L.; total proteins, 7.0 gm.%; albumin, 5.0 gm.%; globulin, 2.0 gm.%; prothrombin time, 90%; total cholesterol, 170 mg.%; cholesterol esters, 115 mg.%; blood ureau nitrogen, 16.4 mg.%. The fat content of the stools was 4.3%. The protein-bound iodine was 7.9 μg/100 ml., and the 24-hour uptake of I^{131} was 29%, with a conversion ratio of 28%. An initial basal metabolic rate of plus 67 was unreliable; when repeated after therapy, it was plus 10. The

TABLE 1

Blood Calcium and Phosphorus

Date	Ca mg. %	P mg. %	Alk. Phos. Bodansky Units	Treatment
3/28/57	4.4	6.3	—	
4/3/57	5.6	7.4	0.1	*4/5/57:*
4/8/57	7.2	7.6	1.4	Vit. D, 150,000 U/D
4/10/57	6.6	7.8	1.3	Ca gluconate, 12 gm./D
4/12/57	7.4	6.5	1.9	Low P diet
4/15/57	8.2	—	3.2	
4/17/57	7.4	6.1	1.3	
4/19/57	7.4	6.7	2.9	
4/22/57	7.8	5.6	1.8	
4/24/57	8.5	5.6	2.7	
4/29/57	8.5	6.5	1.7	
5/1/57	8.9	4.7	0.7	
5/3/57	9.4	6.1	0.3	*5/3/57:*
5/6/57	8.7	3.8	2.2	Amphojel R,
5/8/57	9.0	6.1	—	15 c.c. t.i.d.
5/10/57	9.2	5.6	2.6	*5/9/57:*
5/13/57	8.5	5.6	2.5	Vit. D, 200,000 U/D
5/17/57	9.6	5.3	0.9	

urinary 17-ketosteroid excretion was 7.1 mg.; the 17 OH corticosteroid excretion, 7.3 mg. per 24 hours. The electrocardiogram on admission revealed prolongation of the QT interval to 0.42 second, mainly due to lengthening of the ST segment. The electro-encephalogram on admission revealed normal voltage; absence of alpha rhythm, a basic rhythm of six per second, and slow waves of four per second in all leads seen best on hyperventilation.

The patient's course in the hospital was remarkable in several respects. Prior to the initiation of specific therapy she experienced many episodes daily of painful spasms of the muscles of the extremities, neck and trunk, with carpopedal spasm, extension of the legs and arching of the back. There were periods of unresponsiveness during which she appeared to be awake, and other periods lasting for several hours during which she was in a comatose state. These inactive periods alternated with restlessness and attacks of tetany.

Therapy was begun with oral administration of 12 gm. calcium gluconate and of 150,000 units of vitamin D_2 (calciferol) daily. The patient was given a diet free of dairy products. Serum calcium, inorganic phosphorus and alkaline phosphatase

were determined three times weekly, and Sulkowitch's test was done frequently. The level of serum calcium rose gradually, and became nearly normal (8.5 mg.%) after three weeks of therapy, but the serum phosphorus level remained elevated (5.6 mg.%). Aluminum hydroxide gel, 15 ml. three times daily, was therefore added to the regimen. The daily dose of vitamin D was increased to 200,000 units five weeks after therapy was begun because the serum phosphorus level still remained somewhat elevated (table 1).

The patient's clinical response to therapy was rapid and one of steady improvement. Within 72 hours there was a noticeable decrease in muscular tonicity, so that movements became less jerky and better coördinated. The frequency and severity of the recurrent attacks of tetany began to decrease. She became more alert and her speech more intelligible, and all aspects of mental function showed improvement. On the sixth day of therapy the neurologic examination revealed an alert patient and intact orientation, but there were impairment of retention and recall, and inability

FIG. 2. The patient on admission (left) and six weeks after therapy was begun (right).

to concentrate and to perform simple arithmetic problems. She had poor insight concerning her illness and current events. She manifested a moderate degree of intellectual retardation. By the fifth day she was having only slight tetanic spasms, but muscle tone and coördination of movements were normal. Chvostek's and Trousseau's signs had disappeared; she was able to walk well, but with a stooped posture due to a kyphoscoliosis. Her speech was clear, although she spoke with a choppy lisp that had been a lifetime characteristic. At the end of one week all evidence of tetany had completely disappeared and the neurologic findings were normal, with the exception of moderate intellectual deficiency which was consistent with her ability prior to this illness. She began to take an active interest in her appearance and became an energetic, pleasant helper on the ward. At the end of six weeks her weight had increased to 102 pounds, and there was a noticeable regrowth of hair (figure 2).

Subsequent electro-encephalographic studies revealed a change three weeks after therapy was begun from the generally slow activity to one of generalized paroxysmal

dysrhythmia in the form of bursts of 6/second waves, slowing to 4/second on hyperventilation. This abnormal activity was somewhat improved with the appearance of some alpha rhythm five weeks after the clinical manifestations of tetany, and her mental state had cleared. At the same time the electrocardiogram improved, so that about 12 days after the onset of therapy the hypocalcemic changes were less marked, and three weeks later the electrocardiogram was entirely normal (five weeks after the onset of therapy).

Discussion

This patient presents many of the classic features of hypoparathyroidism. The mental picture and tetany were striking. The alopecia, history of convulsions, and cataract, and the roentgenographic, electrocardiographic and electroencephalographic changes are not unusual. Features which are common but which this patient did not manifest are papilledema, increased intracranial pressure, and trophic changes of skin and nails. The absence of digestive and hematologic disturbances and the presence of low blood calcium, low alkaline phosphatase, high phosphorus and normal amounts of fat in the stools permitted the exclusion of tetany associated with steatorrhea. There was no evidence of kidney disease or of pseudohypoparathyroidism, and no history of thyroid surgery or neck irradiation. Finally, the thyroid, adrenocortical and gonadal functions were normal. Thus the monoglandular nature of the insufficiency involving solely the parathyroids was established. Hypoparathyroidism associated with insufficiency of other endocrine glands has been reported by Perlmutter et al.[7] (1956), Whitaker et al.[8] (1956) and Leonard[9] (1946). There was no evidence of moniliasis. In the absence of any detectable cause, the case was classified as idiopathic hypoparathyroidism.

The most noteworthy feature of this case is the rapid and complete clinical recovery following an unusually prolonged and severe course of mental deterioration. The patient had had a moderate degree of intellectual deficiency prior to the onset of the disease, and this original level of mental function became evident after adequate therapy. Mental deterioration had apparently begun three years prior to admission and was progressive, leading to severe impairment of sensorium and mental function in all spheres. She manifested noticeable improvement within 72 hours after therapy was instituted, two weeks before the serum calcium reached even the low limit of normal and when the phosphorus level was still very high. This response is unusual, since most patients with such mental changes require several weeks or longer to return to their previous mental state. Indeed, a case has been reported by Mortell[10] (1946) in which there was no change in the pronounced mental symptoms while other features improved with treatment. Idiopathic hypoparathyroidism may be associated with such symptoms as depression, excitement, toxic delirium, personality changes of various types, intellectual deficiency, mental deterioration, mental dullness and impairment of sensorium as described by Grant[3] (1953), Sugar[4] (1953), de Mowbray[5] (1953), Robinson et al.[6] (1954) and Simpson[11] (1952). These mental changes have not been reported as the initial symptoms, and are usually manifest only after prolonged hypocalcemia in idiopathic hypoparathyroidism.

Postoperative hypoparathyroidism is commonly associated with an early onset of mental symptoms constituting a toxic psychosis as reported by Sugar[4] (1953),

de Mowbray [5] (1953) and Greene [18] (1941). Greene [18] pointed out that delirium, which may be followed by dementia, may be the first and only clinical manifestation of postoperative hypoparathyroidism, and that it improves rapidly with a return of the electrolytes to normal levels. The cause of the mental changes is not known.

Tetany is the most common presenting symptom of idiopathic hypoparathyroidism, as reported in 70% of the 57 cases in the literature reviewed by de Mowbray [5] (1953). Alopecia appeared to be the earliest symptom in our patient, since it began 12 years prior to the onset of painful muscle cramps. The increased density of bones seen in our patient is occasionally found in hypoparathyroidism. It may well be that the unusually long duration of the disease prior to therapy caused the increased mineral content of bones to reach a level permitting detection in the roentgenogram.

Seizures are the second most common presenting symptom, according to de Mowbray [5] (1953), occurring in 42% of the 57 cases reviewed. Reports as to the frequency of the occurrence of generalized seizures in tetany differ widely. Simpson [11] (1952) states that seizures are common and may occur prior to the onset of tetany. Sugar [4] (1953), on the other hand, states that most patients with hypocalcemia do not have seizures. The mechanism of production of seizures is unknown. Sugar [4] (1953) discusses the theory that seizures are due to water retention and/or a disturbance in surface function of brain-cell membranes due to the low calcium, which permits the building up of abnormal electrical potentials.

The various aspects of papilledema and seizures were reviewed by Grant [3] (1953), who found the occurrence of convulsions to be the feature most commonly associated with papilledema and tetany, although they may occur without papilledema. Some authors, such as Gotta and Odoriz [12] (1948), believe that the low calcium and elevated phosphorus precipitate seizures in individuals with low thresholds and idiopathic seizure states, but Grant [3] (1953), Gotta [13] (1951) and others do not accept this explanation. Grant [3] (1953) pointed out that the convulsions are controlled by primary therapy of the hypoparathyroidism and not by anticonvulsants.

In this patient's history the occurrence of two convulsions prior to the onset of tetany suggests the possibility of a preëxisting seizure state. However, convulsions were a prominent feature during the first two years of the tetanic illness. No convulsions were recognized during the latter two years, in which the mental symptoms were pronounced. The occurrence of seizures early in the illness was probably responsible for failure to recognize the disease.

The electro-encephalographic changes in hypoparathyroidism have been described by numerous authors including Grant [3] (1953), Sugar [4] (1953), de Mowbray [5] (1953), Simpson [11] (1952), Gotta and Odoriz [12] (1948), Gotta [13] (1951), Grieve [14] (1955) and Odoriz et al.[15] (1944). Abnormal electroencephalographic records are said to be found in over 80% of cases of chronic tetany by Klotz and Stroun [16] (1955), who found that such a record has no practical significance in the differential diagnosis of the cause of tetany. Grant [3] (1953) and others have found that the electro-encephalogram is usually abnormal in chronic hypoparathyroidism, with or without the occurrence of seizures. There are no characteristic changes, but usually there are little or no alpha

rhythm, an occasional increase in the amount of fast activity, simple spikes and, commonly, slowing to from three to seven waves per second. Hyperventilation accentuates these and brings out latent changes. There is no exact correlation between the electro-encephalographic changes and the serum calcium, but the duration of the hypocalcemia appears to be more important than the calcium level. The electro-encephalogram returns to normal several weeks after the serum calcium and phosphorus have been maintained at normal levels (Grant [3] (1953); Sugar [4] (1953) and Schulman and Ratner [17] (1955)). Often the degree of improvement in the electro-encephalogram is incomplete after treatment (Sugar [4] (1953)). Grant [3] (1953) stated that this delayed response suggests an intracellular fluid and metabolic disturbance that require readjustment.

The electro-encephalographic changes of our patient conform to those described by others. It is of interest that after three weeks of adequate treatment the pattern changed from a generally slow record to one of generalized paroxysmal cerebral dysrhythmia which persisted throughout the remainder of the hospitalization. Whether the persistently abnormal electro-encephalographic record is indicative of a preëxisting epileptic state or secondary to permanent changes within the brain is uncertain.

Although papilledema due to increased intracranial pressure has been reported in cases of long standing idiopathic hypoparathyroidism, it is said by Grant [3] (1953) to be relatively rare. Our patient illustrates the fact that mental symptoms may be pronounced without elevated intracranial pressure. Cataracts resulting in decreased visual acuity are a common feature of this disease and may be the presenting symptom (de Mowbray [5] (1953)). A cataract was found in the left eye, but the patient herself failed to report decreased vision. Headaches may be severe, as reported by Simpson [11] (1952), but were absent in our patient.

Extrapyramidal dyskinesias, such as hypertonicity and choreiform movements, have been reported in hypoparathyroidism by Simpson [11] (1952) and Gsell [19] (1950). These features were present in our patient and were accentuated by attempted voluntary movements, especially walking. These signs cleared rapidly with treatment.

Intracranial calcifications are not unusual in postoperative hypoparathyroidism, but are relatively rare in the idiopathic form, according to Sugar [4] (1953) and Burghardt [20] (1953). Originally, following the early descriptions by Pick [21] (1902) and Fahr [22] (1930), it was thought that the tetany was the result of the cerebral calcifications, but the cerebral lesions are now generally considered to be caused by hypoparathyroidism (Sugar [4] (1953) and Wagner et al.[23] (1954)); however, the mechanism is not known. In roentgenograms the calcifications are usually seen as bilaterally symmetric collections of fine-to-heavy densities in the area of the basal ganglia, as was the case in our patient. The pathologic findings at autopsy on patients with idiopathic as well as postoperative hypoparathyroidism have been reported by Sugar [4] (1953), Burghardt [20] (1953), Wagner et al.[23] (1954), Eaton and Haines [24] (1939), Eaton et al.[25] (1939), and Jordan and Kelsall [26] (1951). The changes are chiefly those of hyalinization and calcification of capillaries and smaller arteries and veins, predominantly in the caudate and globus pallidus, but to a slightly lesser extent in the putamen, dentate nuclei, and occasionally in other areas of the brain. The calcium deposits are located chiefly in the adventitia and media of the vessels, but some may be seen free in the parenchyma.

Degeneration and loss of ganglion cells have been reported in areas of the basal ganglia where the vascular degeneration is severe (Sugar [4] (1953)). Why the basal ganglia are primarily involved is not known, but Sugar [4] (1953) postulated that the characteristics of the circulation in these areas may be pathogenetically related, since these are also the areas involved in disease states producing cerebral hypoxia. The occurrence of calcification in the basal ganglia is not restricted to hypoparathyroidism, and is not necessarily accompanied by neurologic symptoms. There seems to be no correlation between the clinical picture and the degree of calcification. The calcification has not been reported to regress following therapy.

The electrocardiographic changes characteristic of hypocalcemia reverted to normal only when the blood calcium level became normal. This special behavior of electrocardiographic changes due to hypocalcemia has previously been recorded by White et al.[27] (1929) and Barker et al.[28] (1937), and more recently by Schulman et al.[17] (1955). The dissociation between the response of tetany and of the electrocardiogram to calcium administration was reported by Sussman et al.[29] (1957).

Summary

A case of idiopathic hypoparathyroidism occurring in a young woman is presented. The four-year duration, pronounced severity and relative completeness of symptomatology and rapid recovery are of interest. The clinical features of this condition are discussed.

Summario in Interlingua

Es presentate un caso de hypoparathyroidismo idiopathic, occurrente in un femina de racia blanc de 30 annos de etate. Aspectos de interesse es que le morbo habeva durate quatro annos quando illo esseva diagnosticate, que le symptomatologia esseva relativemente complete e sever, e que le restablimento del patiente esseva rapide.

Al initio—i.e. quatro annos ante le admission del patiente al Hospital del Collegio Medical Jefferson a Philadelphia—le morbo esseva characterisate per perdita de capillo. Attaccos de tetania generalisate de severitate e frequentia progressive e convulsiones generalisate predominava durante le sequente duo annos. Disturbation de omne aspectos del functionamento mental deveniva apparente e progredeva in le curso de tres annos usque a grados sever de deterioration. Durante le quarte anno le patiente esseva incapace de ambular a causa de spastic movimentos torsional de su trunco e de su extremitates. Illa non poteva attender a su exigentias personal, e su parola esseva inintelligibile. Su historia medical revelava un annue perdita partial de capillo depost le etate de 14 annos, le perdita del complete dentatura al etate adolescente, e duo pregnantias sin incidente que habeva occurrite septe e cinque annos ante le hospitalisation.

Le examine del patiente revelava le sequente significative constatationes anormal: Un peso de 86 libras, alopecia quasi complete, imperfectiones de comprehension e attention, responsas tardive, disorientation, deterioration intellectual, parola dysarthric, opacitate del lente sinistre, hypertonicitate e movimentos dyscinetic del trunco e del extremitates, e positive signos de Chvostek e Trousseau. Le patiente habeva frequente generalisate spasmos tetanic de grado sever, e su stato de conscietate alterava inter semistupor e coma. Aspectos del morbo que es commun sed que non esseva manifeste in le presente caso es papilledema, augmentate pression intracranial, alterationes trophic del pelle e del ungulos, e moniliasis.

Le constatationes laboratorial que esseva congruente con le diagnose de hypoparathyroidismo includeva un basse nivello sanguinee de calcium, un basse nivello de phosphatase alcalin e un alte nivello de phosphoro, le alterationes electrocardiographic typic de hypocalcemia, calcification intracranial in le area del ganglios basal, e un generalmente lente activitate electro-encephalographic. Varie altere examines excludeva specificamente le possibilitate de steatorrhea, morbo renal, e altere dysfunctiones endocrin.

Le therapia consisteva del administration oral de gluconato de calcium, vitamina D_2 (calciferol), e un dieta libere de productos lactee. Subsequentemente, gel de hydroxydo de aluminium esseva addite al regime proque tres septimanas post le initiation del medication le phosphoro del sero monstrava ancora nivellos elevate. Le plus notabile aspecto de iste caso es le rapide restablimento clinic post un inusualmente longe e sever maladia. Melioration symptomatic esseva recognoscibile in omne respectos intra 48 horas. Illo esseva complete intra un septimana, con le exception del recrescimento de capillo e le augmento del peso corporee. Istos progredeva rapidemente. Le melioration clinic precedeva le restitution de nivellos normal de calcium e phosphoro in le sero. Le normalisation de iste magnitudes requireva tres e sex septimanas, respectivemente. Le electro-encephalogramma e le electrocardiogramma attingeva lor maximos de melioration tres septimanas post que le calcium del sero habeva redevenite normal. Le moderate residue defectuositate mental que persisteva es probabilemente un phenomeno que esseva presente ante le declaration del symptomas de hypoparathyroidismo.

Un revista del litteratura pertinente al aspectos clinic de hypoparathyroidismo idiopathic es presentate. Le datos es discutite in connexion con le aspectos correspondente del presente caso.

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COLD SENSITIVITY SYNDROME*

By Edwin E. Goldberg, Captain, U.S.A.F.R. (MC), *Decatur, Illinois,* and Dobson R. Pittman, Captain, U.S.A.R. (MC), *New York, N. Y.*

Hypersensitivity to cold has received insufficient attention as a definite clinical entity. The syndrome is not uncommon, despite the fact that only scattered case reports have appeared in the literature since the original description by Beheir in 1866. Familiarity with the syndrome assumes increasing impor-

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From the 6604 U.S.A.F. Hospital, A.P.O. 862, New York, N. Y., the Department of Medicine, Veterans Administration Westside Hospital, and the Department of Medicine, University of Illinois College of Medicine.
Requests for reprints should be addressed to Edwin E. Goldberg, M.D., 510 Standard Office Building, 132 South Water Street, Decatur, Illinois.

tance today with the establishment of military and civilian populations in cold climates.

Case Report

A 19 year old white male of German descent was referred to the 6604th U. S. Air Force Hospital from an Arctic Air Force Base on September 17, 1956, for evaluation of "an atypical Raynaud's phenomenon." The patient had been completely asymptomatic until two years prior to admission, at which time he experienced mild frostbite of his hands while throwing snowballs. At that time he developed rubor.

Fig. 1. (*above*) Ring finger of left hand following exposure at 35° F. for 20 minutes. Note edema of the entire finger and "pinching" by wedding band.

Fig. 2. (*below*) Same finger five hours later with patient at room temperature. The normal, ample fit of the ring has been emphasized by placing a match stick underneath it.

numbness, and swelling of both hands following a two-hour exposure to extremely cold air and snow. No ulcers or skin changes were noted at the time. His hands apparently returned to normal after "thawing out."

Since this episode he has discovered that upon exposure to even moderately cold conditions (35° F. or below), his hands swell, hurt and turn red. In addition to these symptoms he develops large wheals with pruritus on the extensor surfaces of his wrists, under his eyes, and on his chest, trunk and back. There is no blanching or cyanosis of his hands.

The patient's history is negative for other allergic or sensitivity reactions. Antihistaminic drugs have not modified his disease. He has no history of syphilis or urinary color changes. The attacks are not related to exercise. He has never smoked and does not drink. There is no pertinent family history.

Physical examination was essentially normal, and no changes were noted in the skin or the nails. The peripheral pulses were normal, and the radial and ulnar circulations were adequate according to Allen's test. Dermatographia was not present. Laboratory studies were normal and included the following: serological test for syphilis (cardiolipin), negative; cold agglutinins, negative; direct and indirect Coombs' tests, negative; hemoglobin, 16.5 gm.; hematocrit, 50; sedimentation rate, 1 mm. per hour; total cholesterol, 215 mg.%; total serum protein, 7.2 gm.% (albumin, 5.25 gm.%, globulin, 1.95 gm.%); leukocyte count, 7.3 thousand per cubic millimeter, with a normal differential. Blood type B, Rh positive. Urinalysis was negative. Roentgenogram of the chest was normal. Cryoglobulins were tested for by aspirating venous blood and allowing it to clot at room temperature. The serum was then removed and refrigerated at 3° C. for 24 hours. No precipitation was observed.

The following tests were performed on the patient. The patient immersed one hand in ice-water. No blanching or cyanosis occurred, but rubor was present almost immediately. After 45 seconds he complained of a "numb, burning sensation" in his fingers. In 60 seconds he complained that his fingers were beginning to feel stiff. After two and a half minutes he "could not feel" his fingers, but his hands were "warm and burning," and his wrists and forearm hurt. In five minutes the hand was removed from the water, and marked rubor was present. No other changes were noted in the patient's body. His hand began to ache upon removal from the water, and continued to do so for the next 10 minutes. There was no urticaria, but the wrist and hand were visibly swollen. One of the authors subjected his hand to the same environment with the following differences: rubor and pain were more marked in the patient; blanching on pressure following removal from ice-water lasted 10 times as long in the patient (50 seconds), and the control hand returned to normal within two minutes, whereas the patient's hand took 10 minutes to return to normal. Control blood pressures and pulse rates were taken with the patient sitting at room temperature.

Control Blood Pressure, Right Arm	Pulse
150/90	88
154/110	86
130/90	84
Average 144/96	*Average* 86

The patient's hand was then immersed in ice-water for five minutes and the blood pressure and pulse rate were recorded at intervals.

Blood Pressure, Right Arm	Time	Pulse
100/70	1½ Minutes	104
100/70	2½ Minutes	112
190/100	4 Minutes	116
120/90	5 Minutes	116

Note that in the control period the blood pressure in the right arm averaged 144/96 mm. of Hg, and that within two and one-half minutes after the immersion of the hand in ice-water there had been a fall of 44 mm. of Hg in the systolic blood pressure and 26 mm. in the diastolic. Likewise, the pulse had risen 22 beats per minute during this period above the average control rate of 86. In normal individuals this test produces a mild rise in both systolic and diastolic blood pressure without a change in pulse rate. In individuals with a hyperactive sympathetic nervous system, and in many patients with essential hypertension, there is a significant rise in systolic and diastolic pressure, the pulse rate remaining unchanged.

The patient was exposed to a mean temperature of 35° F. dressed in normal clothing without an overcoat or gloves. After 20 minutes of exposure his hands and fingers began to swell, and there was marked itching and burning. Figure 1 was taken after this exposure. No urticarial wheals of the face or body were observed at this time. It should be noted that after he had rested at room temperature it took some five hours for the patient's hand to return to normal (figure 2).

Discussion

The syndrome of hypersensitivity to cold is frequently overlooked because of its mild manifestations. The patient who experiences minimal whealing and a mild pruritus only when the temperature goes below a certain mean, and only after prolonged exposure, rarely sees a physician. On the other hand, some individuals are acutely sensitive to cold and experience a sudden rapid fall in blood pressure and peripheral vascular collapse on exposure to cold air or water. These patients are unable to tolerate cold showers because of weakness and syncope. It has been stressed that fatal accidents by drowning may well occur if sensitive individuals go swimming in cold water.[1, 2]

Even where only local reactions occur there can be hazards, as in the case of a young woman who suffered severe choking spells after eating icecream. A wide variety of clinical symptoms has been seen in this syndrome. Localized pain, swelling or redness may occur only at the point of contact with cold, or there may be a generalized systemic reaction, with giant urticaria, pruritus, flushing, decrease in gastric acidity, joint pains, tachycardia and syncope.[3] Eosinophilia is rare, but has been seen in association with this syndrome.[4] Electrocardiographic abnormalities with changes in the direction of the T waves and premature ventricular beats have been reported.[5, 6]

A strong family history can sometimes be elicited, and there are reports of large numbers of cases occurring in a single family over several generations.[7, 8, 9] Kelly and Wise [3] have stated that patients with a familial history differ from sporadic cases. In these cases symptoms date from infancy, joint pains and fever are commonly present, exposure to cold produces generalized whealing without pruritus, and the syndrome is not reproducible with locally applied ice or ice-water.

Many of the symptoms of hypersensitivity to cold have been seen in association with other diseases, notably syphilis. More recently there have been reports of cold hypersensitivity in patients with essential cryoglobulinemia. In these cases, in addition to hypersensitivity to cold, purpura and Raynaud's phenomenon are commonly present, and of course cryoglobulins are demonstrable on exposing the serum to cold.[10]

The etiology of this interesting syndrome has not been clearly defined in spite of much excellent experimental work. Cold hypersensitivity unassociated with other systemic disease has been attributed to an increased reactivity of the normal response of the peripheral vascular tree to cold, as first described by Sir Thomas Lewis. In normal individuals, rapid reduction in the skin temperature to 10 to 15° C. for twenty seconds will usually produce flaring and wheal formation. With lower temperatures and increased length of exposure, redness, blisters and increase in volume of the exposed part are noted. Lewis postulated that these changes are due to the release of a diffusible histamine-like substance from injured cells of the superficial epidermis. In cold-sensitive subjects there is an exaggerated response, and these changes are observed at higher temperatures and after a shorter period of exposure.[4] Previous tissue injury, specifically by cold, may be of significance. Other authors have attributed the syndrome to a defect in the heat-regulating mechanism of the body.[11] Some of the reported cases appear to be definitely allergic in origin. The presence of a definite family history and eosinophilia would favor this. Passive transfer by the Prausnitz-Küstner method has been demonstrated in some cases,[12] and would tend to incriminate a transferable antibody, or at least to suggest the presence of a cold reagin. However, not all cases demonstrate this phenomenon.[13]

Some patients have been reported to have an excellent response to antihistamine therapy[14] or histamine desensitization, even when cold antibodies could not be demonstrated.[15] On the other hand, even when passive transfer of cold sensitivity is definitely present, resistance to antihistaminic drugs frequently occurs. In this regard it is interesting to note that in a typical case of cold hypersensitivity the reaction was temporarily blocked by intravenous adrenocorticotrophic hormone.[2] A case of cryoproteinuria with associated cold hypersensitivity has been reported in which treatment with cortisone resulted in disappearance not only of the symptoms of cold sensitivity but also of serum cryoprecipitation on exposure to cold.[16]

The patient presented is interesting for several reasons. He showed some of the characteristics predominantly seen in cases with a familial history. Thus he reacted with generalized urticaria when exposed to cold, and failed to experience the complete syndrome when ice or ice-water was applied locally. On the other hand, the recent onset of his symptoms (after local cold trauma to his hands two years ago), a negative family history and the total absence of fever would point more to the sporadic type of cold hypersensitivity. Another interesting facet of the case was the onset of his symptoms at a relatively high temperature (35° F.). While his symptoms were much more marked at lower temperatures, even at this temperature the patient was incapacitated by marked edema and stiffness of his hands, so that it was impossible for him to drive a truck or do any manual work. Because of his severe symptoms and failure to benefit from antihistamines, he was removed from the Command.

Summary

A case of hypersensitivity to cold has been reported. The literature has been reviewed, and some of the possible mechanisms of this syndrome have been presented.

Summario in Interlingua

Hypersensibilitate pro frigida, ben que rarmente describite in le litteratura, es un entitate clinic non incommun. Le syndrome es de importantia considerabile in vista del establimento de colonias militar e civil in regiones de climate frigide.

Le symptomas varia ab prurito e vibices in leve casos usque a subite reductiones del pression de sanguine e collapso del vasculatura peripheric in casos sever. In casos de sensibilitate acute, il existe le definite hasardo de necation quando le subjecto es exponite a aqua frigide e mesmo de suffocation quando ille ingluti un substantia que es troppo frigide.

Un extense varietate de symptomas clinic ha essite vidite in iste syndrome. Dolores localisate, tumescentia o rubor occurre in certe casos solmente al puncto de contacto con le fonte de basse temperaturas, sed in altere casos il occurre un generalisate reaction systemic, con urticaria gigante, prurito, rubor, reduction del aciditate gastric, dolores articular, tachycardia, syncope, eosinophilia, e anormalitates electrocardiographic.

Un forte historia familial es demonstrabile a vices, con plure casos occurrente in le curso de multe generationes. In altere casos, le syndrome es sporadic. Le syndrome ha essite incontrate in association con altere morbos, notabilemente syphilis, e recentemente illo ha essite describite como presente in casos de cryoglobulinemia e cryoproteinuria essential. Le etiologia del syndrome ha non ancora essite definite clarmente. In individuos normal, le abrupte reduction del temperatura cutanee pote producer rubor, vibices, pustulas, e augmento del volumine del parte exponite—secundo le grado del frigor e le duration del exposition. Il ha essite postulate que iste alterationes es causate per un diffundibile substantia histaminoide que es liberate per injuriate cellulas del epidermis superficial. In certe subjectos qui es sensibile pro frigido, il occurrerea un responsa exaggerate, e le alterationes de iste responsa supervenirea a minus basse temperaturas e post minus prolongate periodos de exposition. In altere casos, un definite historia familial, le presentia de eosinophilia, e le demonstration del phenomeno de transferimento passive tende a supportar le interpretation que il se tracta de un responsa allergic.

Le tractamento del syndrome non es satisfacente. Certe patientes responde a antihistaminas o a dissensibilisation de histamina, sed iste responsa non pote esser correlationate con le presentia o le absentia de cryo-anticorpore. Therapia a steroides pare esser de valor in certe casos. Tamen, le grande majoritate del patientes pare resister a omne formas de therapia. Tal subjectos debe esser distantiate ab le fonte del stimulos de frigor si on vole supprimer lor symptomas.

Es describite le caso de un patiente de 19 annos de etate qui habeva iste syndrome. In iste patiente, le historia familial e le historia allergic esseva negative. Duo annos post le experientia de leve grados de pernion in le manos, ille disveloppava grande vibices e prurito generalisate durante un periodo de servicio militar a un base del fortia aeree in le arctica. Le examine physic esseva pauco inusual, e le tests laboratorial esseva omnes normal. Tests serologic pro syphilis esseva omnes negative, e cryoglobulinas non poteva esser demonstrate in le sero. Le immersion del manos del patiente in aqua glaciate durante duo minutas e medie produceva un reduction per 44 mm de Hg in le tension de sanguine systolic e de 26 mm de Hg in le tension de sangine diastolic, durante que le frequentia del pulso ascendeva a 22 supra le lectura de controlo. Quando exponite a un temperatura de 35 F durante 20 minutas, le patiente disveloppava marcate grados de edema, prurito, e un sensation de arditura in le digitos que retornava al stato de normalitate post cinque horas de reposo al temperatura normal de interior. A causa del severitate de su symptomas e a causa del refuso de su organismo de responder al tractamento, le patiente debeva esser evacuate ab le posto.

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CORONARY EMBOLUS WITH MYOCARDIAL INFARCTION AND RUPTURE*

By Armand P. Gelpi, M.D., *San Francisco, California,* and Norman Ende, M.D., *Fresno, California*

Coronary occlusion due to embolic phenomena is a relatively rare occurrence. Two recent excellent reviews [1, 2] have covered the subject of coronary embolism in great detail, and it is not the purpose of this paper to duplicate such a survey of the literature. Recently we encountered a case of coronary embolism which

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From the Medical and Laboratory Services, Veterans Administration Hospital, Fresno, California.

Requests for reprints should be addressed to Armand P. Gelpi, M.D., Veterans Administration Hospital, Forty-second and Clement Streets, San Francisco, California.

resulted in a small myocardial infarction and a perforation of the left ventricle. These unusual complications, along with other interesting features of the case, serve as the basis for this report.

In a perusal of the literature for a similar case we encountered a publication by Bopp in 1926 [3] describing a case of sclerosis of the left coronary artery with an obstruction of the lumen which was apparently caused by a calcareous mass that the author felt was embolic in origin. The patient died suddenly with a ruptured heart, but the source of the embolus was not indicated in his report. This case of cardiac rupture associated with embolism was the only one described in Saphir's review of 1933,[4] and we have been unable to find similar cases in subsequent publications.

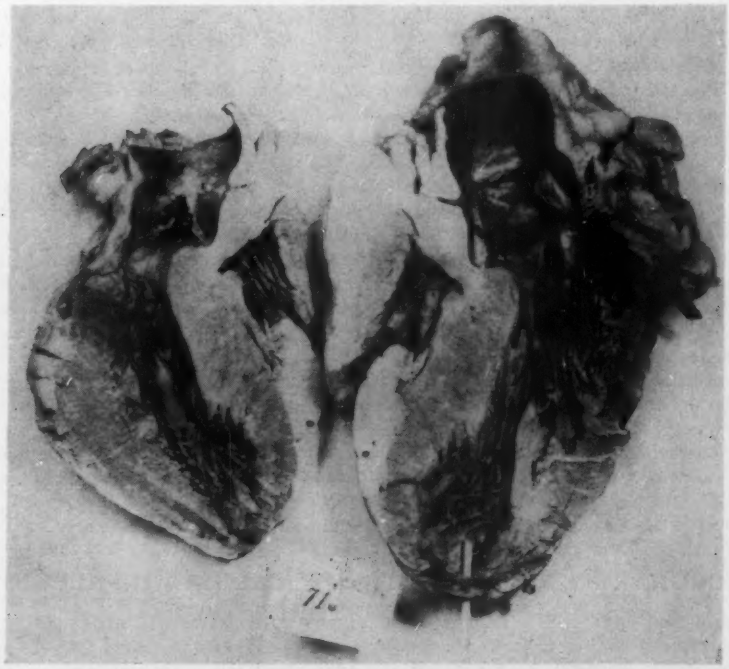

FIG. 1. Longitudinal section of the heart, showing myocardial infarction and perforation.

CASE REPORT

A 66 year old white male entered this hospital with a referral diagnosis of ulcerative colitis on June 2, 1956. The patient had symptoms of recurrent diarrhea and melena which had existed since February, 1956. He had recently been hospitalized elsewhere for a period of six weeks, during which time he received two blood transfusions and a variety of supportive medications. For two weeks he had been taking 5 mg. of Meticorten four times a day. On the day before admission the patient had the onset of rather severe right-sided pleuritic chest pain, which had subsided over a period of 24 hours, and he reported that he had had one other such episode of pain

several weeks previously. Since the onset of his colitis he estimated that he had sustained a 50-pound weight loss. The past history indicated that the patient had had a kidney ailment accompanied by chills, fever and dysuria in 1954.

The physical examination revealed a well developed elderly man who was afebrile and apprehensive, and showed signs of chronic illness, including weight loss. The skin and mucous membranes showed a moderate pallor; no significant lymphadenopathy was noted. Examination of the eyes, ears, nose and throat was not remarkable. The lungs were clear to percussion and auscultation. The heart seemed slightly enlarged to percussion. The heart rhythm was regular, the sounds were of good quality, and no murmurs were heard. The pulse was regular at 100; blood pressure, 120/80 mm. of Hg. Good pulsations were felt in all four extremities. Homan's sign was negative in both legs, and there was no local calf tenderness; a trace of pitting edema

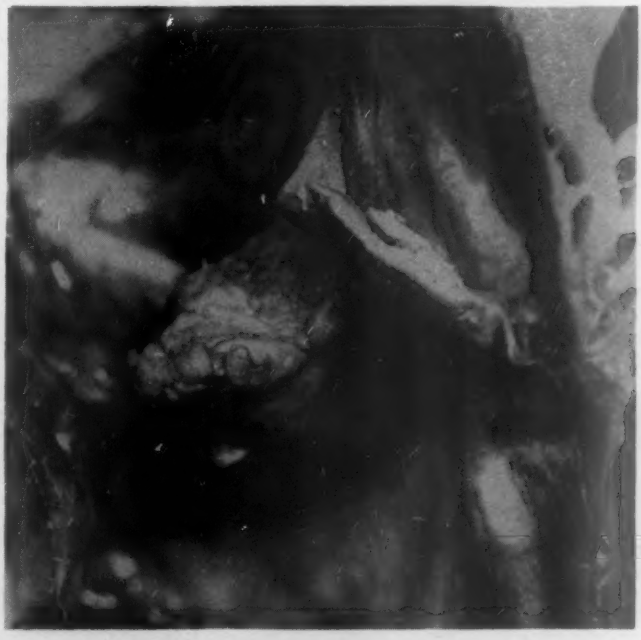

FIG. 2. Close up view of aortic valve, showing vegetations on the right posterior cusp.

of the ankles was present. There were no abdominal masses or tenderness. Rectal examination revealed large external hemorrhoids, one of which was thrombosed; a small amount of bloody mucus was obtained on the gloved finger.

The white blood cell count was 5,400, with 47% neutrophils, 46% lymphocytes, 3% monocytes, and 4% eosinophils. The hemoglobin was 11.5 gm. and hematocrit was 40%. The urinalysis was normal, and serologic test for syphilis was negative. The bromsulfalein retention was 24% at 45 minutes (normal is less than 5%). Successive stool examinations were negative for the presence of ova and parasites, but were uniformly strongly positive for occult blood. The serum proteins totaled 7 gm.%, with 3.6 gm.% of albumin and 3.4 gm.% of globulin. An x-ray of the chest showed a small circumscribed density above the right diaphragm, but there was no other

evidence of parenchymal disease or cardiac enlargement. A barium enema showed the classic appearance of ulcerative colitis; in addition, pseudopolypoid changes were seen after evacuation. A sigmoidoscopic examination showed an intensely congested, friable, bleeding mucous membrane throughout the rectum and the rectosigmoid.

Treatment consisted of a high-protein, low-residue diet, a trial of amebicidal therapy which consisted of chloroquine diphosphate and carbarsone for 10 days, and additional supportive treatment including several blood transfusions. The Medicorten was tapered off during the first two weeks of his hospitalization. There was no obvious response to these measures, and the patient continued to have frequent bloody stools, abdominal cramps and malaise. Because of the failure of medical manage-

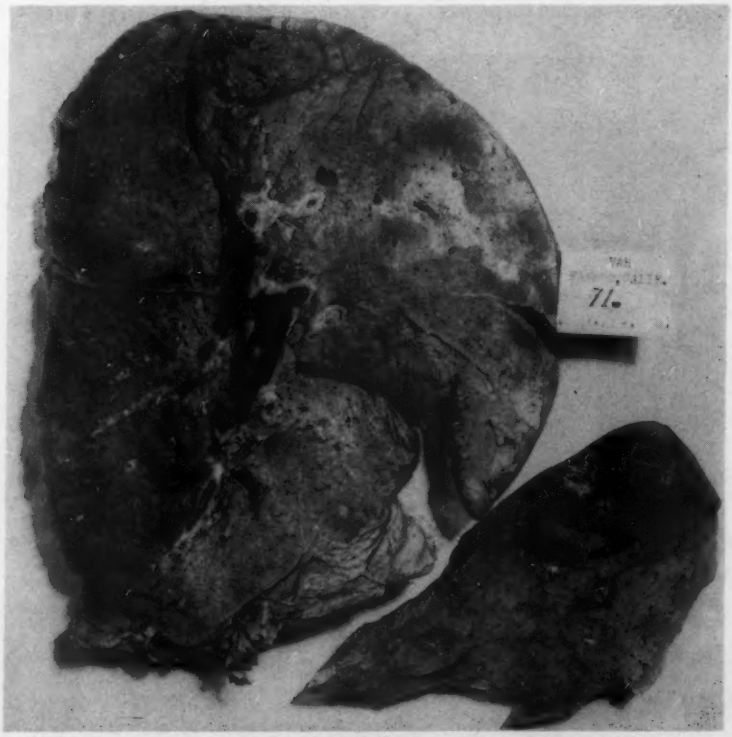

FIG. 3. Abscesses in both upper lobes, with adjacent pneumonic consolidation.

ment and the x-ray evidence of advanced colitis, the patient was prepared for an elective colectomy. On July 12, 1956, he developed an acute thrombophlebitis of the right leg, with the simultaneous occurrence of pleuritic chest pain. An electrocardiogram taken on this date showed a small, 0.02-second duration "Q" wave in Leads III and aVF, with slight "T" wave inversion in Lead III. Swelling and tenderness of the leg rapidly subsided after treatment with a parenteral trypsin preparation. After a three-week period of further observation it was felt that the patient could withstand surgery. On August 7, 1956, he underwent a total colectomy. The surgical specimen had changes of moderately advanced ulcerative colitis with some

small pseudopolyps. The immediate postoperative course was essentially uncomplicated. The patient received extra supportive treatment with intravenous Hydrocortone in decreasing doses until his last dose of 5 mg. on August 14, 1956. On the same day he began to have a spiking temperature, with elevations as high as 101° F. daily, and complained of right-sided abdominal pain. Physical examination revealed no obvious cause for the temperature except slight drainage from the operative wound. Antibiotic treatment was instituted on August 17, 1956, with penicillin, 600,000 units every two hours, streptomycin, 0.5 gm. every six hours, Achromycin, 200 mg. every six hours intravenously, and neomycin, 1 gm. every six hours orally. X-rays of the chest showed an infiltration in the right midlung field and two small circumscribed infiltrates in the left upper lung field. On August 17, 1956, the white blood cell count was 76,000 with 96% neutrophils, 3% lymphocytes and 1% eosinophils. Over the next four days the patient's condition deteriorated rapidly. He developed jaundice, dyspnea, profuse diaphoresis, and a cough productive of thick mucoid secretion. On August 20, 1956, the blood urea nitrogen was 30 mg.%, and the CO_2 combining power was 15.4 mEq. per liter.

Material from the abdominal wound was cultured on August 21, 1956, and grew out *Staphylococcus aureus*. The organism by the disc method was insensitive to penicillin, streptomycin, the tetracyclines, bacitracin, polymyxin and erythromycin. It was sensitive to neomycin, Chloromycetin, Cathomycin, Enterobiotic and Furacin.

The patient died suddenly on August 21, 1956. Prior to embalming a culture of the left lung was taken under sterile technic.

Autopsy Findings: At autopsy the patient's skin was noted to be icteric. The abdomen had a partially healed midline wound 20 cm. in length. An ileostomy and a colostomy were also present. When the peritoneal cavity was opened purulent material was encountered in the abdominal wall surrounding the surgical wound; there was, however, no evidence of diffuse peritonitis.

The pericardial cavity contained 250 c.c. of clotted blood. The heart weighed 400 gm. The pulmonary artery had no evidence of thrombi. The aortic valve had a large vegetation of the right posterior cusp measuring 0.8 by 0.8 cm. (figures 1 and 2). When the valve was placed in the closed position the vegetation was just below the ostium of the left coronary artery; the remainder of the valve showed no unusual changes. The coronary vessels showed rigidity with pipestem formation, but with widely patent lumens. The right coronary artery was somewhat smaller than normal and did not have the usual large branches descending down the posterior surface of the heart toward the apex. The left anterior descending artery was widely patent to a point 6 cm. from its origin, where it was occluded by a yellow-red thrombus. The myocardium had an area of red infarction at the apex measuring 3 by 2 cm. Through the center of the infarction there was an irregular hole, 0.4 cm. in diameter, through which blood could be easily expressed (figure 1).

The right pleural cavity contained 500 c.c. of bloody fluid, and there was fibrin on the surface of the right lower lobe. The left pleural cavity contained 50 c.c. of bloody fluid. The right lung weighed 800 gm. The tracheobronchial tree contained a moderate amount of mucopurulent material. The bronchial mucosa was red. A multiloculated abscess cavity was found in the right upper lobe measuring approximately 2 by 3 by 3 cm. (figure 3). The left lung weighed 700 gm. An abscess cavity measuring 2 by 3 by 2 cm. was encountered in the left upper lobe. The liver was diffusely enlarged and weighed 2,700 gm. The spleen weighed 500 gm. and had a tense capsule. The large bowel, except for the rectal stump, was absent. No other significant abnormalities were noted in the peritoneal cavity. Each adrenal weighed 13 gm. and appeared to be congested. The right kidney weighed 250 gm., and its capsule stripped with difficulty to reveal a pale, relatively smooth surface

with an occasional red spot. There was a normal corticomedullary ratio. The left kidney weighed 200 gm. and was similar to the right. No other significant gross pathology was noted in the remainder of the autopsy.

In sections taken from the myocardium through the area of infarction there were extravasated erythrocytes separating the myocardial fibers (figure 4). In this area the myocardial fibers had poorly discernible or absent cross striations, the nuclei were indistinct, and there were focal collections of neutrophils. In a section taken of the left anterior descending coronary artery the lumen was filled with a blood clot and in this clot there was a crescent-shaped area filled with coccoid bacteria (figure 5).

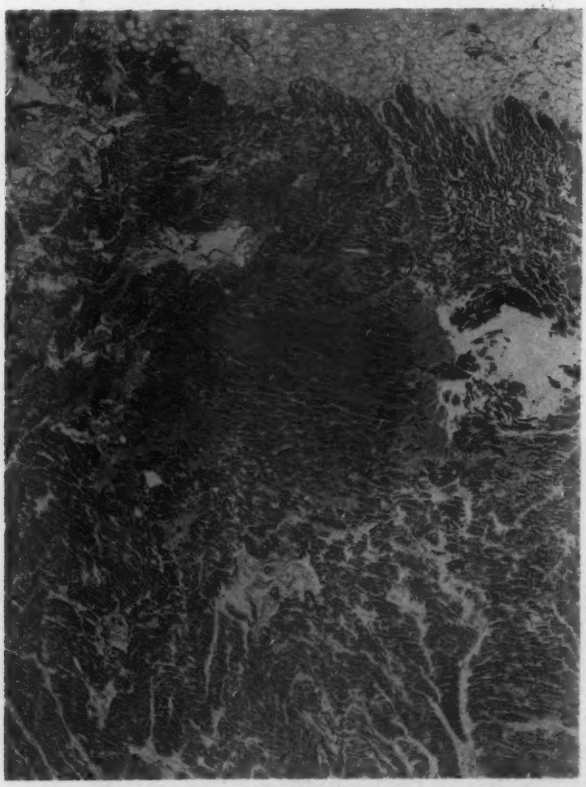

FIG. 4. Myocardial infarction, with extravasated blood between the muscle fibers.

The adventitia surrounding the vessel had a heavy infiltration of neutrophilic granulocytes, and there was a slight infiltrate of similar cells into the media.

In sections taken from the wall of the pulmonary abscess cavity there were masses of neutrophilic granulocytes, and only ghosts of alveolar structures could be detected. Numerous clumps of bacteria were present. Smears made of pus from both lungs at the time of autopsy showed gram-positive cocci.

The liver had a diffuse scattering of neutrophilic granulocytes in the sinuses and around the portal triads.

The normal architectural pattern of the spleen was not well demarcated, and the sinuses contained numerous neutrophils. The malpighian corpuscles were poorly discernible.

The adrenals had markedly congested and dilated blood vessels, but there was no evidence of extravasation. There was a moderate number of inflammatory cells in the deeper portions of the cortex.

The capsule of the kidney was thickened and infiltrated with numerous lymphocytes and neutrophilic granulocytes. The cortex had some evidence of nephrosclerosis

FIG. 5. Photomicrograph showing crescent-shaped mass of bacteria and thrombus filling the lumen of the coronary artery.

with hyalinized glomeruli. In addition, there were focal collections predominantly of neutrophilic granulocytes in the interstitial tissues of the cortex, and similar inflammatory cells were noted in some of the adjacent tubules. The remainder of the microscopic examination revealed no other significant pathologic findings.

The culture taken of the left lung after death grew out a hemolytic *S. aureus* having the identical antibiotic sensitivity as the organism cultured from the abdominal wound.

Discussion

Several aspects of this patient's illness deserve comment. While the occurrence of ulcerative colitis late in life is unusual, the disease does appear after the age of 60 in a small percentage of patients. In one of the largest reported series of ulcerative colitis, 2.2% of the patients had the onset of the disease at the age of 60 or beyond.[5]

It is known that thrombophlebitis is a not uncommon complication of chronic ulcerative colitis.[5] In the case cited here the episodes of chest pain occurring earlier in the illness can be explained on the basis of pulmonary emboli from a deep thrombophlebitis of the leg. From the microscopic examination of the myocardium, the infarction did not appear to be more than a few days old. There is therefore no reason to relate the earlier history of chest pain to coronary artery disease; furthermore, during the last few days of illness the patient did not complain of chest pain, despite the occurrence of a coronary occlusion.

Although atherosclerosis of the coronary arteries was evident, the major vessels were widely patent except at the site of the embolic occlusion. The lack of collateral circulation may explain in part why a relatively small area of infarction resulted in myocardial rupture. Hamman, in discussing coronary embolism,[6] pointed out that because of the absence of a collateral blood supply, the immediate prognosis was poor when a major coronary occlusion developed in an otherwise healthy coronary arterial system.

It is problematic whether the postoperative support with hydrocortisone predisposed the patient to developing a bacteremia, nor is it likely that an early recognition of the organism as a staphylococcus resistant to most antibiotics would have averted the sudden death of this particular patient.

It has become increasingly evident within the last few years that the staphylococcus has probably become second in importance only to *Streptococcus viridans* as the cause of bacterial endocarditis. In the review of staphylococcic endocarditis prepared by Dowling et al.,[7] the ratio of streptococcus to staphylococcus cases appeared to be 2.6:1. Levinson et al.[8] have reported an incidence of 28% staphylococcal etiology from a total of 64 consecutive cases of bacterial endocarditis. It is noteworthy that postcommissurotomy septic endocarditis is characteristically caused by the staphylococcus.[9, 10]

Unfortunately, cultures of the valvular vegetation could not be taken from our patient at the time of autopsy. However, the proximity of the vegetation to the left coronary ostium, as pointed out in the protocol, and the demonstration of coccoid forms in the embolus, leave little room for doubt that the organism was the same as that cultured from the lung and from the operative wound. The fact that the antibiotic sensitivity of both cultures was identical would lend support to the premise that the entire pathologic picture was caused by one organism.

Summary

A case of septic coronary embolism has been presented in which death resulted from myocardial rupture at the site of infarction. The patient developed a postoperative wound infection due to an antibiotic-resistant staphylococcus following colectomy, with resultant metastatic lung abscesses and an acute bacterial

endocarditis. A fragment of the vegetation on the right posterior aortic cusp occluded the anterior descending branch of the left coronary artery. We were unable to find any similar case of cardiac rupture due to septic coronary embolism.

Summario in Interlingua

Le autores reporta un caso inusual de embolo coronari, occurrente in un patiente post colectomia pro intractabile colitis ulcerative.

Un masculo de 66 annos de etate habeva habite symptomas de diarrhea e melena durante cinque menses e non respondeva a un regime supportative, a steroides adrenal, o a un essayo de therapia amebicidal. Le maladia esseva complicate per le disveloppamento de un thrombophlebitis del gamba dextere e de infarction pulmonar. Examines sigmoidoscopic e roentgenographic del intestino crasse revelava signos typic de colitis ulcerative. Iste signos esseva ancora apparente quando le colon esseva resecate. Le curso post-operatori esseva complicate per un infection del vulnere, causate per *Staphylococcus aureus,* que se provava resistente al majoritate del antibioticos disponibile. Le patiente moriva subitemente.

Le examine necroptic revelava que le causa immediate del morte esseva un ruptura myocardial que habeva occurrite post infarcimento. Le descendente arteria coronari sinistro-anterior habeva essite occlusionate per un embolo septic de origine in un vegetation fresc al cuspide aortic dextero-posterior. In plus, duo abscessos pulmonar esseva demonstrabile. Ab illos, hemolytic *Staph. aureus* esseva culturate, con un comportamento de resistentia antibiotic identic con illo del organismo isolate ab le inficite vulnere. Le embolo coronari monstrava massas de organismos coccoide in le examine microscopic.

Un revista del litteratura confirma le raritate de embolismo coronari. In le previemente reportate casos, le morte occurreva ante que le infarcimento myocardial poteva disveloppar se a grados notabile. Le autores crede que le hic describite caso es le prime publicate exemplo de ruptura myocardial causate per septic embolismo coronari.

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EDITORIALS

PROPOSED CHANGES IN THE CONSTITUTION AND THE BY-LAWS OF THE AMERICAN COLLEGE OF PHYSICIANS

The attention of all Masters and Fellows of the College is directed to the proposed revision of the Constitution, which is published in this issue as the first item under the section on College News Notes.

The changes in this proposed version of the Constitution and By-Laws were submitted to the Board of Regents by a special Committee under the chairmanship of Dr. Walter L. Palmer. The Regents at their fall meeting voted approval of the changes.

The most important changes proposed appear to be the following:

INCREASED AUTHORITY FOR THE PRESIDENT:

*By-Laws Article III Section 1

The Executive Committee of the Board of Regents has been used by some recent Presidents as an alternate authority in place of the Board of Regents. The proposed change would alter the composition of the Executive Committee by reducing the representation of the Regents from five members "elected by the Regents" to three members "nominated by the President" and elected by the Regents.

By-Laws Article III Section 2

Somewhat similarly, the procedure for the selection of Regents to be members of the Committee on Credentials would be altered from "the Board of Regents shall appoint . . ." to "elected by the Regents on nomination of the President."

The President in the present By-Laws is an ex-officio member of certain standing Committees. In the revised form he would be a voting member.

THE BOARD OF REGENTS:

By-Laws Article II Section 1

The Board would be enlarged by three members by a new provision: "A past President shall serve one term of three years as Regent, and shall not be eligible for re-election."

The term of office of each Regent would be potentially lengthened from six to nine or more years. In the present By-Laws, Article II, Section 3 reads: "The Members of the Board of Regents shall each serve for a term of three years

* These references are to the text of the revised version of the Constitution and By-Laws.

and not more than two consecutive terms." In the proposed version, this would read: "The elected members of the Board of Regents shall each serve for a term of three years for not more than three consecutive terms, exclusive of any unexpired fraction of a term previously served."

By-Laws Article II Section 2

CHANGES IN THE ADMINISTRATIVE OFFICE OF THE COLLEGE:

Under the present By-Laws (Article I, Section 1), the Executive Secretary is named as one of the officers of the College. Under Article I, Section 9, the Executive Secretary's duties under the direction of the Board of Regents are outlined.

The changes made in the proposed version are of a permissive character, to give to the Regents greater flexibility in the future organization of the administrative staff. The wording is as follows: "The Board of Regents shall appoint a Chief Administrative Officer or Officers, with such assistants as the Board may deem advisable, and by whatever title or titles the Board may designate."

By-Laws Article I Section 10

By-Laws Article I Section 1

In the new listing of the Officers of the College, the "Chief Administrative Officer" is not included.

It is apparent that the proposed changes indicate a trend toward concentration of authority in fewer hands, and toward perpetuation in office. It is very possible that by such means more speedy handling of the numerous details of the business of the College may be attained. It is, however, worthy of careful consideration by the whole membership of the College as to whether, viewed impersonally as policy, these trends meet with their approval.

In accordance with the Constitution and By-Laws, the proposed alterations and amendments will be submitted to the vote of the membership at the Business Meeting during the coming General Sessions of the College.

MAURICE C. PINCOFFS, M.A.C.P.

RECENT ADVANCES IN THE STUDY OF MEASLES VIRUS

MEASLES was first transmitted artificially from man to man in 1758 by Home,[1] who exposed skin incisions of nonimmune volunteers to blood from patients ill with the disease. In 1905 Hektoen [2] injected fresh blood from patients with measles subcutaneously into two individuals who developed measles 11 and 13 days later, respectively. Susceptibility of species of the genus *Macaca* was established by the experiments of Goldberger and Anderson in 1911,[3] when they demonstrated that more than 50% of monkeys inoculated with blood and nasopharyngeal washings from patients with measles developed fever, catarrhal symptoms and exanthem. Transmission of this disease through six passages in monkeys was accomplished by subinoculation of blood. Blake and Trask [4] confirmed these findings using unfiltered nasopharyngeal washings, and further noted that the illness in the simian host frequently was associated with leukopenia and lesions of the buccal mucosa. The filtrable nature of this agent was also demonstrated by these workers. The cultivation of measles virus in tissue culture was first described by Plotz in 1938.[5] Propagation of the agent of measles in embryonated hens' eggs was reported in 1939 by Rake and Shaffer, who were able to produce disease in monkeys after serial egg passage.[6] Continued passage of egg-adapted virus resulted in attenuation of the disease for man and monkeys; however, attempts to immunize man with this attenuated virus were inconclusive. Further studies on the active immunization of man with measles virus antigens were discontinued in the United States following this apparent failure.

Thus, although the viral origin of measles had been suspected for some time, precise definition of the biologic properties of the causative agent was not possible until 1954, when Enders and Peebles described the isolation of measles virus in tissue culture.[7]

The propagation of measles virus has led to the demonstration of characteristic and somewhat unique cytopathogenicity, antigenicity of tissue-culture adapted virus and specific antibody in the serum of patients previously exposed to measles virus. Various workers subsequently have confirmed

[1] Home, F.: Medical facts and experiments, Gentleman's Magazine and Historical Chronicle **28**: 285, 1758.

[2] Hektoen, L.: Experimental measles, J. Infect. Dis. **2**: 238–255, 1905.

[3] Goldberger, J., and Anderson, J. E.: An experimental demonstration of the presence of the virus of measles in the mixed buccal and nasal secretions, J. A. M. A. **57**: 476–478, 1911a.

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[5] Plotz, H.: Culture "in vitro" du virus de la rougeole, Bull. Acad. de méd., Paris **119**: 589–601, 1938.

[6] Rake, G., and Shaffer, M. F.: Propagation of the agent of measles in the fertile hen's egg, Nature, London **144**: 672–673, 1939.

[7] Enders, J. F., and Peebles, T. C.: Propagation in tissue cultures of cytopathogenic agents from patients with measles, Proc. Soc. Exper. Biol. and Med. **86**: 277–286, 1954.

these findings,[8, 9, 10] and it is now well established that measles virus can be propagated serially in a variety of tissue-culture cell lines.

Enders and Peebles were able to demonstrate cytopathogenicity in human and monkey renal cell cultures inoculated with blood and throat washings from patients during the early acute phase of measles infection. These authors isolated eight strains of virus from uncomplicated illnesses and one strain from the lung of a patient who died during the acute stage of the disease. Cohen and her co-workers [8] have described the isolation of three additional strains of measles virus from uncomplicated cases of the disease, and Ruckle and Rogers [9] have demonstrated virus in blood and throat washings from nine of 25 patients. In Ruckle's experience, negative isolation attempts were associated with the presence of antibody, which may explain her failure to recover virus from the cerebrospinal fluid and blood of nine patients with central nervous system symptoms developing from three to six days after the onset of rash. More recently, the isolation of measles virus from lung tissue of patients dying with giant-cell pneumonia has been reported.[10]

In all instances, viral activity in tissue culture has been characterized by the appearance of syncytia, or multinucleated giant cells, which frequently contain eosinophilic intranuclear inclusions and eosinophilic cytoplasmic masses. In addition, fusiform or stellate cells may be observed. As the process continues, all of the cells become involved and eventually are destroyed. To date, measles virus has been propagated in human kidney and amnion, monkey and canine renal cells,[7, 10] the KB line of human carcinoma cells,[11] the Hep-2 and HeLa lines of human carcinoma cells,[12] and the FL line of human amnion [13] and human heart cells.[14] It appears that primary isolation of measles virus is best accomplished with human or monkey renal cells and primary human amnion cells, although the use of FL cells for this purpose has been described.

In addition to providing an efficient, inexpensive method of isolating and characterizing the causative agent of measles, tissue-culture technics permit

[8] Cohen, S. M., Gordon, I., Rapp, F., Macaulay, J. C., and Buckley, S. M.: Fluorescent antibody and complement-fixation tests of agents isolated in tissue culture from measles patients, Proc. Soc. Exper. Biol. and Med. **90**: 118–122, 1955.

[9] Ruckle, G., and Rogers, K. D.: Studies with measles virus. II. Isolation of virus and immunologic studies in persons who have had the natural disease, J. Immunol. **78**: 341–355, 1957.

[10] Girardi, A. J., Warren, J., Goldman, C., and Jeffries, B.: Growth and CF antigenicity of measles virus in cells deriving from human heart, Proc. Soc. Exper. Biol. and Med. **98**: 18–22, 1958.

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[13] Frankel, J. W., and West, M. K.: Cultivation of measles virus in a stable line of human amnion cells, Proc. Soc. Exper. Biol. and Med. **97**: 741–742, 1958.

[14] Frankel, J. W., Burnstein, T., and West, M. K.: Propagation of measles virus in tissue cultures of dog kidney cells (abstract), Federation Proc. **17**: 551, 1958.

the study of inapparent infection, naturally acquired immunity and host response to artificial immunization, by measurement of specific antibody. Neutralizing and complement-fixing antibodies appear in the serum of patients with measles soon after the onset of the exanthem, and may reach a high level 10 days later. Neutralization titers in human beings during convalescence range from 1:160 to 1:512, complement-fixing titers range from 1:32 to 1:512.[6] The convenience and simplicity of the complement-fixation test make it the procedure of choice for routine diagnostic purposes. Experience to date reveals a fairly good correlation between historical and antibody findings. Antibody studies performed in the author's laboratory have revealed that 80% of persons over the age of 15 years possess complement-fixing antibody. The geometric mean titer in this group of 250 individuals was 1:30. Whether measles antibody persists at this level in the adult host in the absence of extrinsic antigenic stimulation has yet to be determined. The rate of acquisition of antibody closely paralleled the attack rate of clinically overt measles. Passively acquired maternal antibody was readily demonstrable in cord blood, and in many instances its concentration was higher than that of the mother's blood. Congenitally acquired antibody apparently degrades beyond measurable amounts by the third month of life in most instances. Whether this is the point at which the infant becomes susceptible to infection is doubtful, since few cases of measles are observed in children less than one year of age. Furthermore, completely protective doses of gamma globulin do not result in the circulation of measles antibody in amounts measurable by currently available technics. Where neutralization and complement-fixation tests were performed on the same serum specimen, correlation between these tests approached 100%. Studies now in progress may be expected to provide answers to the problems of inapparent infection with measles virus and the relationship of circulating antibody and immunity to this disease.

Of greatest importance are those studies which have a direct bearing on the production of an effective and safe immunizing agent. The need for such a vaccine cannot be disputed in view of the mortality associated with such complications of measles as encephalitis and pneumonia. It has been estimated that one child in 1,000 with measles develops encephalitis, and approximately 35% of these either die or suffer from permanent neurologic residua. In addition, total morbidity expressed in terms of student-days lost from school, cost of hospitalization and physician care assumes tremendous proportions during epidemic years. Therefore, prevention of measles with a vaccine which results in a durable immune state is a worthwhile goal.

The experiments of Enders and his co-workers [15] provide the prototype with which studies of measles vaccines may be performed. These authors

[15] Enders, J. F., Peebles, T. C., McCarthy, K., Milovanovic, M., Mitus, A., and Holloway, A.: Measles virus: a summary of experiments concerned with isolation, properties and behavior, Am. J. Pub. Health 47: 275–282, 1957.

have shown that cynomolgus monkeys inoculated with measles virus cultivated in human tissue develop a disease not unlike measles infection in man. Animals inoculated by both the intravenous and the intranasal routes developed viremia four or five days later which persisted for from two to five days. An exanthem and a leukopenia were noted soon after the viremic phase. Shortly after the rash had cleared, complement-fixing antibodies appeared in the blood. Antibodies still were detectable after eight months. In addition to the observation that some monkeys failed to develop all of these features of measles infection, it was demonstrated that some were solidly immune to the initial challenge. This resistance to induced infection was associated with the presence of antibody which had been acquired prior to the first intentional exposure to measles virus. The agent responsible for these antibodies may be human measles virus spread spontaneously to monkeys held in close association with man, or a simian virus which produces natural disease. The absence of antibody in recently captured monkeys seems to support the former concept. Further studies in Enders' laboratories have confirmed earlier findings that measles virus will multiply in the developing chick embryo. After several passages in eggs, cytopathogenicity upon subculture in human amnion cells could be demonstrated.

More recently, the adaptation of measles virus to chick-embryo cell culture has been reported.[16] Cytopathogenicity for chick cells was not demonstrable until the fifth passage in these cells and, beginning with the sixth passage, there was a marked increase in growth rate. This change in cytopathogenicity and rapidity of growth in chick-embryo cell culture coincided with an attenuation of measles virus for the monkey. Of great interest is the observation that monkeys receiving the chick-cell adapted virus not only failed to show evidence of illness but also resisted subsequent challenge with measles virus capable of producing disease in normal animals. Following inoculation with attenuated virus, monkeys developed complement-fixing and neutralizing antibodies which persisted for at least five and one-half months.[17] Exposure of the immune animals to virulent virus resulted in an increase of circulating antibody.

At the present time, two potential measles vaccines are on the horizon. Measles virus propagated in monkey renal-cell cultures can be rendered noninfectious with formalin in much the same fashion as poliovirus vaccine is produced. The problems of monkey supply and contamination of cell cultures with simian viruses are conspicuous disadvantages of this type of vaccine. Furthermore, infectivity titers of measles virus in monkey-kidney culture are of a low order, and it is likely that more antigenic mass than has been achieved to date will be needed if an inactivated vaccine is used. Although higher virus titers can be obtained in continuous cell lines, it is

[16] Katz, S. L., Milovanovic, M., and Enders, J. F.: Propagation of measles virus in cultures of chick embryo cells, Proc. Soc. Exper. Biol. and Med. **97**: 23–29, 1958.

[17] Katz, S. L., Medearis, D. N., Jr., and Enders, J. F.: Experiences with a live attenuated measles virus (abstract), Am. J. Dis. Child. **96**: 183–184, 1958.

unlikely that this source of vaccine will be acceptable because of the presumed malignant nature of these cells. If chick-cell adapted measles virus proves to be attenuated for man with retention of antigenicity, it may offer American physicians an opportunity to lose some of their trepidation about the use of living vaccines. The outstanding advantage of a living, attenuated vaccine generally is its capacity to produce durable immunity after a single inoculation. This should be the case with attenuated measles vaccine. The questions of antigen stability, immunogenicity and host reaction to measles vaccines have yet to be answered. Hopefully, a safe and effective preparation may be a reality in the near future, thus marking the beginning of control of measles through active immunization.

F. R. McCrumb, Jr., M.D.

REVIEWS

Clinical Endocrinology. 2nd Ed. By KARL E. PASCHKIS, M.D., ABRAHAM E. RAKOFF, M.D., and ABRAHAM CANTAROW, M.D. 941 pages; 24 × 16 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, N. Y. 1958. Price, $18.00.

This book is divided into sections dealing with each of the endocrine glands; sections on obesity and pregnancy are also included. Each section consists of a chapter on the anatomy and physiology of the particular organ and then follow chapters dealing with the clinical disorders of hyperfunction and hypofunction. The material is well organized and easy to read. Most of the advances in knowledge made in the last few years have been included; where controversial issues are involved, both sides of the argument are usually presented fairly. An exception to the latter is in discussion of the treatment of diabetic coma where it is not mentioned that excess infusions of sodium chloride may lead to hypernatremia nor that the main value of infusions of glucose is to maintain extracellular fluid volume and prevent secondary collapse. There will be disagreement also with the recommendation of extensive subtotal thyroidectomy for nodular goiter without mentioning the efficacy of medical suppressive therapy with thyroid hormone.

It is stated that no patient with Addison's disease should be permitted to have elective surgery; actually with proper preparation such patients withstand operations quite well. There is an obvious printing error on page 189: the calculation of the dose of radioiodine should be in microcuries and the dose given should be in millicuries.

Apart from minor criticisms such as those just mentioned, the book on the whole has much to recommend it. The bibliography is extensive and includes recent publications; there is a final section devoted to the most modern methods of hormonal analyses and to various diagnostic laboratory tests; the index is very good. With so few good textbooks on endocrinology available, this one is a notable contribution and should prove to be very valuable both to the student and to the practicing physician.

J. G. W.

The Relation of Psychiatry to Pharmacology. By ABRAHAM WIKLER, M.D. 322 pages; 25.5 × 17.5 cm. (paper-bound). The Williams and Wilkins Company, Baltimore. 1957. Price, $4.00.

The printing of this volume was subsidized by the American Society for Pharmacology and Experimental Therapeutics. It is one of the most important and certainly one of the most useful general reference works on the relation of psychiatry to pharmacology. It is authoritative and abreast of recent advances. The book is divided into two main sections: (1) the effect of drugs on human behavior, and (2) the theories and mechanism of drug actions. Some of the more important drugs, such as tranquilizers, mood elevators, anesthetics, psychosomimetic agents, analeptic agents, and insulin, which are used at the present time in therapy, are included. A most valuable portion of the book, and the section that represents a notable effort of collection, verification, and compilation, is that section devoted to the theories and mechanism of drug action.

The book is clearly written in spite of the difficult and relatively complicated material which is discussed. Detailed explanations with numerous examples are included. On the whole the book represents a valuable analysis and compilation on the timely problem of drug action on behavior.

The author has cited 889 references on the relation of psychiatry to pharmacology. The general conclusion is especially well written and is fraught with portents of future developments between the disciplines of pharmacology and psychiatry.

JOHN C. KRANTZ, JR.

Electrocardiogram Clinics. By JOSEPH E. F. RISEMAN, M.D., and ELLIOTT L. SAGALL, M.D. 259 pages; 24 × 31 cm. The Macmillan Co., New York, N. Y. 1958. Price, $10.50.

One inherent difficulty in the usual electrocardiographic textbook is the problem of incorporating adequate discussions and correlations of the electrocardiogram with clinical material. The usual text, of which there has been a veritable deluge in recent years, pays only lip service to the necessity for evaluating the electrocardiogram on the general background of the patient.

In *Electrocardiogram Clinics,* the authors present the tracings, case histories, and questions on clinical management contributed by the participating physicians in a Post Graduate Course entitled, "E.K.G. Clinics." The discussions were tape recorded, edited and used as the basis for this book. The histories are critically discussed, the tracings interpreted in detail, and the material utilized for both clinical correlation and a critical analysis of the problems raised.

This book fulfills needs not met by other standard texts. It furnishes electrocardiograms and discussions which can be utilized by physicians as an aid in electrocardiographic instruction. However, it is not meant as a substitute; but as a supplement for standard texts. The present volume has clinics devoted to angina pectoris, myocardial infarction, and pulmonary embolism. It is hoped that additional clinics will be published in the near future.

L. S.

Pharmacology in Medicine: A Collaborative Textbook. 2nd Ed. Edited by VICTOR A. DRILL, Ph.D., M.D. 1273 pages; 28.5 × 22 cm. McGraw-Hill Book Co., Inc., Blakiston Division, New York. 1958. Price, $19.50.

The fine reception given to the first edition of this popular textbook when it appeared in 1954, and the amazing advances in pharmacology and therapeutics during the last four years have necessitated a new edition of this encyclopedic work. Like the previous edition, each chapter is the contribution of a recognized authority in his field. The present edition consists of 19 major parts and 88 separate chapters, by a total of 86 collaborators. In editing the vast amount of material in a book of these dimensions by so many collaborators, Dr. Drill has done a fine job in organizing and keeping the style as uniform as possible. A notable improvement, in this reviewer's opinion, is the numbering of pages consecutively, instead of the chapter-page numbering system which was so confusing in the first edition. The chapters in the second edition have been revised and brought up to date, and new references have been added. A new section on Psychopharmacology, with a chapter by Dr. Peter B. Dews on "Drugs Affecting Behavior," is a fine addition to this timely subject.

The book is beautifully printed, two columns to the page, in easy-to-read type on good quality paper. The diagrams, tables and chemical formulas (which are given for all principal drugs) are nicely proportioned and neatly executed. An especially valuable feature of the book is the extensive bibliography at the end of each chapter. The full title to each reference is given, making it easy for students and investigators to locate pertinent works for further reference. The book is comprehensive, authoritative, and as up-to-date as it is possible for a medical textbook to be in this age of rapidly advancing medical science. The reviewer enthusiastically recommends it to teachers, students, research workers and practitioners desiring a reference work that will furnish them with information on practically any therapeutic substance in use today.

R. M. B.

Poisoning: A Guide to Clinical Diagnosis and Treatment. 2nd Ed. W. F. von Oettingen, M.D., Ph.D. 627 pages; 24 × 16 cm. W. B. Saunders Co., Philadelphia. 1958. Price, $12.50.

The second edition of this book, which was originally published in 1952, is a revision which incorporates discussion of the toxic effects of the newer commercial and drug products which have appeared since the earlier publication. In addition, there are included discussions of preparations which were available in 1952 but were omitted from the first edition probably because of lack of information concerning their toxic effects. It is not possible, in this review, to list the additional compounds described, but the fact that this edition has 127 more pages devoted to discussions of individual compounds and mixtures is an index of the extent of the revision.

The arrangement of the text is the same as in the first edition with the contents divided in four parts, i.e., Introduction; Diagnosis; Management; Symptoms and Treatment of Various Types of Poisoning. The section on diagnosis includes a description of the structural and functional pathological changes observable in poisonings by various agents. These are described according to different organ systems and under each pathological condition there is an alphabetical list of the substances which have been reported to have caused the change. This should prove useful when one is searching for possible causative agents producing a given clinical picture.

There is also included in the section on diagnosis, a chapter devoted to chemical tests for poisons in the blood and urine. Although the author prefaces his description of these tests with the statement that definite identification of a poison can be made only by relatively involved procedures, this chapter may cause those unfamiliar with the problems of analytical toxicology to fall into error. Most of the tests described are non-specific and their use would presuppose knowledge of the identity of the substance sought. Some of the tests, for example that for lead in urine, are below the limits of sensitivity for the concentration of the substance found in cases of poisoning.

The last section of the book, dealing with the toxic effects of individual substances is, by far, the most valuable section. In this, the substances are arranged alphabetically and under each there is a discussion of reported toxic reactions. Each description is annotated with literature references which compensate for the brevity of some of the presentations.

Considering the book as a whole, it is an excellent presentation of a most difficult subject. It should be an essential part of any library devoted to toxicology as well as a useful reference in the clinician's library.

Henry C. Freimuth

Epilepsy. By Manfred Sakel, M.D. 204 pages; 21.5 × 14.5 cm. Philosophical Library, New York. 1958. Price, $5.00.

This is the posthumous publication of an incomplete manuscript, presented without editorial revision by the author.

The first half of the volume is a general presentation of epilepsy and consists largely of rather old concepts overlaid by a thin veneer of the more recent knowledge of the last two decades.

The second half of the volume presents the author's concepts of idiopathic epilepsy as a disease. Dr. Sakel made a major contribution in the introduction of insulin shock therapy in psychiatry, but his theories as to the rationale of this therapy have received little general acceptance. In the present volume, he presents these theories in some detail and a very similar theory is proposed for an understanding of the "disease," epilepsy.

According to Sakel, there are two "life drives," the anabolic (static) drive, and the catabolic, spendthrift (kinetic) drive. The vital function of the vegetative nervous system is conducting, regulating and controlling the life processes. The

convulsion is looked upon as a "self-defensive reflex mechanism" and is "caused by a sudden unaccountable hyperinsulinemic vagotonia which by a process of reflex reaction, provokes its antagonist and calls upon the defense system to avert the danger threatening the life of the system. The overshooting of the provoked antagonist precipitates a convulsion."

Following this line of thought, Sakel theorized that a "causative treatment" (as opposed to the symptomatic treatment by anti-convulsants) might be achieved by establishing a permanent increased tonus of the "sympathicus" so that a sudden increase in the tonus of the vagus would not result in a convulsion. This he proposed to do by careful transplantation of a piece of thyroid gland from a donor into the thyroid gland of the epileptic. This experiment was carried out in two patients in 1934. In one case he describes remarkable improvement, in the other only temporary improvement, the failure being attributed to resorption of the transplant. These and a few other clinical observations apparently convinced Dr. Sakel of the validity of his theories although he does indicate that further work should be done.

The lack of editorial revision makes the volume rather difficult reading. It is offered by the publishers primarily as a document of historical interest, as Sakel's last contribution to medical literature. It is probable that it would not be of great interest to the general medical public.

JEROME K. MERLIS, M.D.

The Story of Heart Disease. The Fitzpatrick Lectures for 1956 and 1957 given before the Royal College of Physicians of London. By TERENCE EAST, M.A., D.M. (Oxon). 148 pages; 22.5 × 14.5 cm. William Dawson and Sons, Limited, London. 1957. Price, 30s.

The Story of Heart Disease was the subject of the Fitzpatrick Lectures for 1956 and 1957 delivered before the Royal College of Physicians of London. Topics dealt with include diagnosis, pathology, the coronary circulation and its disorders and circulatory failure and its treatment.

The author has attempted to ". . . trace back to its original source some of the knowledge that has come down to us, and see how the first steps were taken; to see if one could gauge how the idea came to its discoverer and how the new knowledge spread and increased." He accomplishes this task by the consideration of separate topics and acquits himself with honor. There are included many carefully selected direct quotations which give the lectures a flavor unusual in most medical historical presentations. "The Coronary Circulation and Its Disorders" is a particularly valuable chapter with a detailed chronological development of the appreciation of coronary artery disease. The references are carefully selected.

This series of lectures is recommended without reservation to students, physicians and historians. From them can be gained an appreciation of many of our concepts in cardiology not readily obtained from the more usual historical sources.

L. S.

Medical Electrical Equipment: Principles, Installation, Operation and Maintenance of Electrical Equipment Used in Hospitals and Clinics. Advisory Editor, ROBERT E. MOLLOY, M.B., F.F.A., R.C.S. 312 pages; 23 × 16 cm. Philosophical Library, Inc., New York, N. Y. 1958. Price, $15.00.

This book attempts to cover all of the applications of electricity to medicine—from the mains that enter a hospital or office to the maintenance of an electroencephalograph machine. The objective is most commendable; it should be done; but, a ten volume loose leaf library will be needed. All of the discussions in this book of about 300 pages are short; most are superficial and convey little; none cover

much more than the introduction to most service manuals that come with the machines described.

B. W. A.

Verhandlungen der deutschen Gesellschaft fur Kreislaufforschung. Band 23: *Kreislauf in Narkose und Hypothermie—Angeborene Herzfehler.* Edited by Prof. Dr. RUDOLF THAUER. 416 pages; 15.5 × 23 cm. (paper-bound). Verlag von Dr. Dietrich Steinkopff, Darmstadt. 1957. Price, brosch. DM 54,–.

The German Heart Association customarily selects specific topics for its annual meeting, and through comprehensive presentations by various speakers an attempt is made to cover most of the newer knowledge of the field. The "Verhandlungen" or proceedings printing the well-edited papers given complete with references and illustrations have thus become a means of reporting the progress of the problems discussed. The twenty-third annual meeting was devoted to the circulation in anesthesia, hypothermia, and congenital heart disease.

Thauer gives a detailed and analytic review of the effect of anesthesia upon circulation, autonomic reflexes, peripheral vasomotor and brain stem directed controls. The bibliography given is extensive.

Brendel presents on the basis of experimental data the effect of hypothermia upon the circulation. The relationship of temperature to pulse rate, cardiac output, pressures, cardiac cycle, etc. are presented. The physiological section is completed by a discussion of the effect of hypothermia upon blood gases. The clinical physiological experiences of anesthesia and hypothermia are given by Sancetta and by Graham, respectively. Both presentations are very informative and lucidly written. A number of ancillary papers of good quality complete the first session.

The second part of the meeting dealing with congenital heart disease is a well-organized review of the field. Embryology (by Toendurg) precedes an interesting discussion of selected points of pathology by Meessen followed by a most informative paper by Grosse-Brockhoff on transformation in the development of clinical features of defect with high pulmonic blood flow. Rossi and Werkoe review the differential diagnosis in all age groups, followed by a discussion of the relative diagnostic value of catheterization and angiocardiography, respectively. Cardiac surgery is ably discussed with clear presentation of the physiological problems encountered in extracorporeal circulation. Several miscellaneous papers of high standard complete the transactions.

The standard of papers given is high, the illustrations and bibliography are excellent. The transactions are an annual addition to the cardiological literature of great value and are highly recommended.

Printing of text and illustrations are of superior quality.

ARTHUR GRISHMAN, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Adénomes Hypophysaires. Rapport Présenté a la Réunion Annuelle de la Société de Neuro-chirurgie de Langue Francaise. Par GÉRARD GUIOT et G. ARFEL, S. BRION, J. CHEGUILLAUME, A. ENNUYER, J. FANJOUX, H. FISCHGOLD, L. GUILLAUMAT, J. METZGER, J.-P. MICHARD, B. THIBAUT, P. TOURNOUX et G. VOURC'H. 276 pages; 25.5 × 16.5 cm. (paper-bound). 1958. Masson et Cie., Paris. Price, 3,800 fr.

L'Angiographie Cérébrale. Travail de la Clinique Neurochirurgicale de la Faculté de Medecine de Marseille et du Service Central de Radiologie de l'Hopital de la Timone (Professeurs Jean E. Paillas et Henri Roux.) Par JOËL BONNAL et JACQUES LEGRÉ; préface du Pr. J. E. PAILLAS. 254 pages; 28 × 18.5 cm. 1958. Masson et Cie., Paris. Price, 6,000 fr.

The Birth of Normal Babies. By LYON P. STREAN, M.Sc., Ph.D., D.D.S., F.A.P.H.A., Consultant, Norristown State Hospital, Norristown, Pa., etc. 194 pages; 22.5 × 14.5 cm. 1958. Twayne Publishers, Inc., New York. Price, $3.95.

Cardiovascular Sound in Health and Disease: Being a Comprehensive Treatise, Introduced by a Historical Survey, Illustrated Mainly by Sound Spectograms (Spectral Phonocardiograms), and Supplemented by an Extensive Bibliography; With a Section on Respiratory Sound. By VICTOR A. MCKUSICK, M.D., Associate Professor of Medicine, The Johns Hopkins University School of Medicine, etc. 570 pages; 27 × 19.5 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, $15.00.

The Clinical Examination of the Nervous System. 11th Ed. By G. H. MONRAD-KROHN, M.D., F.R.C.P., Professor Emeritus of Medicine (Neurology) in the University of Oslo; revised by the author with the assistance of SIGVALD REFSUM, M.D., Professor of Medicine (Neurology) in the University of Oslo, etc. 466 pages; 22.5 × 14.5 cm. 1958. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $9.50.

Concepts and Definitions in the Health Household-Interview Survey: The Design and Content of the Basic Questionnaire, and Preliminary Definitions of Terms Used in Statistical Reports for the Year Ending June 30, 1958. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584–A3. 29 pages; 26 × 20 cm. (paper-bound). 1958. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. Price: For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 30¢.

Difficult Diagnosis: A Guide to the Interpretation of Obscure Illness. By H. J. ROBERTS, M.D., Diplomate of the American Board of Internal Medicine, etc. 913 pages; 24 × 16 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $19.00.

Elements of Biophysics. By JAMES E. RANDALL, B.S.E.E., M.S., Ph.D., Associate Professor of Physiology and Biophysics, Department of Physiology and Pharmacology, University of Missouri Medical Center. 333 pages; 20.5 × 14 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $8.00.

Epilepsy. By MANFRED SAKEL, M.D.; with a preface by OTTO POETZL, Professor Emeritus, University and Clinic of Vienna. 204 pages; 21.5 × 14.5 cm. 1958. Philosophical Library, New York. Price, $5.00.

Handbook of Cardiology for Nurses: Heart Disease and Its Treatment; The Patient and His Nursing Care. 3d Ed. By WALTER MODELL, M.D., F.A.C.P., Associate Professor, Cornell University Medical College, etc.; and DORIS R. SCHWARTZ, B.S., R.N., Assistant Professor, Cornell University-New York Hospital School of Nursing, etc. 328 pages; 21.5 × 14.5 cm. 1958. Springer Publishing Company, Inc., New York. Price, $4.50.

The Love of a Physician: George E. Pfahler, M.D., Pioneer Radiologist. By MURIEL B. PFAHLER. 274 pages; 24 × 15.5 cm. 1958. Dorrance & Company, Inc., Philadelphia. Price, $3.75.

Mental Health Aspects of the Peaceful Uses of Atomic Energy: Report of a Study Group. World Health Organization Technical Report Series No. 151. 53 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Métabolisme de l'Eau dans les Traumatismes du Crâne: Aspects Neuro-endocriniens et Base du Traitement Hormonal: Rapport présenté à la réunion annuelle de la Société de neuro-chirurgie de langue française (1958). Par MM. D. PETIT-DUTAILLIS et E. BERNARD-WEIL. 107 pages; 25.5 × 16.5 cm. (paper-bound). 1958. Masson et Cie., Paris. Price, 1.400 fr.

Pediatric Methods and Standards, Department of Pediatrics, School of Medicine, University of Pennsylvania. 3d Ed. Editor: FRED H. HARVIE, M.D., Associate Professor of Clinical Pediatrics. 324 pages; 20.5 × 12 cm. (loose-leaf). 1958. Lea & Febiger, Philadelphia. Price, $4.50.

Polysaccharides in Biology: Transactions of the Third Conference, May 29, 30, and 31, 1957, Princeton, N. J. Edited by GEORG F. SPRINGER, M.D., William Pepper Laboratory of Clinical Medicine and Department of Microbiology, University of Pennsylvania School of Medicine, Philadelphia, Pa. 249 pages; 24 × 16 cm. 1958. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.75.

Quarto Curso de Cardiologia: Electro-vectocardiografia. EDUARDO COELHO, com a colaboração de MANUEL JOAQUIM SOUSA VENTURA, A. SALES LUIS, SALOMÃO SEQUERRA AMRAM, A. BORDALO E SÁ, A. LOPES PIMENTA E FERNANDO DE PÁDUA. 380 pages; 25 × 17 cm. (paper-bound). 1958. Centro de Estudos de Cardiologia do Instituto de Alta Cultura, Faculdade de Medicina de Lisboa, Lisbon, Portugal.

Recent Advances in Cerebral Palsy. Edited by R. S. ILLINGWORTH, M.D., F.R.C.P., D.P.H., D.C.H., Professor of Child Health, University of Sheffield, etc.; with a foreword by NORMAN B. CAPON, M.D., F.R.C.P., F.R.C.O.G., Professor Emeritus of Child Health, University of Liverpool. 413 pages; 24 × 16 cm. 1958. Little, Brown and Company, Boston. Price, $10.00.

Recent Advances in Paediatrics. 2nd Ed. Edited by DOUGLAS GAIRDNER, M.A. (Cantab.), D.M. (Oxon.), F.R.C.P., Paediatrician to Addenbrooke's Hospital, Cambridge, etc. 378 pages; 21 × 14 cm. 1958. Little, Brown and Company, Boston. Price, $9.50.

Services for Children with Epilepsy: A Guide for Public Health Personnel, Prepared by the Committee on Child Health of the American Public Health Association, 1958. 124 pages; 22.5 × 15 cm. (paper-bound). 1958. The American Public Health Association, Inc., New York. Price, $1.50.

So You Have Glaucoma. By EVERETT R. VEIRS, M.D., Chief of the Section of Ophthalmology for the Scott and White Clinic, Scott and White Memorial Hospitals, and Scott, Sherwood and Brindley Foundation, Temple, Texas, etc. 64 pages; 23.5 × 15.5 cm. 1958. Grune & Stratton, New York. Price, $2.75.

Terceiro Curso de Cardiologia: Arritmias. EDUARDO COELHO, com a colaboração de A. BORDALO E SÁ, ANTÓNIO SOUSA BORGES, MÁRIO GOMES MARQUES, EDUARDO DE PAIVA, ARTUR DE OLIVEIRA, SALOMÃO SEQUERRA AMRAM, FERNANDO DE PÁDUA E JOSÉ FILIPE DA COSTA. 319 pages; 24.5 × 16.5 cm. (paper-bound). 1958. Centro de Estudos de Cardiologia do Instituto de Alta Cultura, Faculdade de Medicina de Lisboa, Portugal.

ERRATUM

On page 1276 of the November, 1958, issue of the ANNALS OF INTERNAL MEDICINE, in the review of the book entitled "Abortion in the United States: Report of a Conference Sponsored by the Planned Parenthood Federation of America, Inc.," an error was made in stating that the Conference was under the auspices of the National Committee on Maternal Health. This should be corrected to read, "Planned Parenthood Federation of America, Inc."

COLLEGE NEWS NOTES

NOTICE OF PROPOSED REVISION OF THE CONSTITUTION AND BY-LAWS

THE AMERICAN COLLEGE OF PHYSICIANS

The following Revision, having been duly approved by the Board of Regents, is herewith submitted to the Fellows and Masters of The American College of Physicians in accordance with provisions of the Constitution, Article VI, and of the By-Laws, Article XV, as heretofore in effect. These Revisions will be presented to the Fellows and Masters at the Annual Business Meeting, Chicago, April 23, 1959, for adoption or rejection, in whole or in part.

CONSTITUTION

ARTICLE I

Name

The name of the corporation shall be the American College of Physicians.

ARTICLE II

The American College of Physicians, hereinafter called the College, is incorporated under the Laws of the State of Delaware. The location of the corporate office is 1306 Broom Street, in the City of Wilmington, County of New Castle, Delaware. The name of the agent therein and in charge thereof is Lewis B. Flinn, M.D.

ARTICLE III

Objects

Section 1. The object of the College shall be to establish an organization composed of qualified internists of high standing who shall meet from time to time for the purpose of considering and discussing medical and scientific topics, and who through their organization shall attempt to accomplish the further purposes of: (a) maintaining and advancing the highest possible standards in medical education, medical practice and research; (b) preserving the history and perpetuating the best traditions of medicine and medical ethics, and (c) maintaining both the dignity of Internal Medicine and the efficiency of its function in relation to public welfare.

Powers

Section 2. Acting through its Board of Regents and Officers, subject to the powers and restrictions of its certificate of incorporation, its Constitution and its By-Laws, the College is empowered to do all and only such acts as are necessary or convenient to the attainment of the objects and purposes herein set forth, and to the same extent and as fully as any natural person might or could do; to purchase, lease, hold, sell, mortgage, or otherwise acquire or dispose of real or personal property; to enter into, make, perform or carry out contracts of every kind with any firm, person, corporation or association; to do any acts necessary or expedient for carrying on any or all of the objects and purposes of the corporation not forbidden by the

certificate of incorporation, or its By-Laws, or by the Laws of the State of Delaware; to have offices and promote and carry on its objects and purposes within or without the State of Delaware, in other States, the District of Columbia, Hawaii, Puerto Rico, the Canal Zone, the Provinces of Canada, Cuba, Mexico and the Central American Republics. The corporation shall not have any capital stock, nor shall it be conducted for the purpose of financial profit.

Section 3. The corporation shall consist of Masters and Fellows hereinafter defined.

Section 4. The corporation may establish other types of membership in the College; such members, however, shall not be members of the corporation or have a right to vote.

Section 5. The corporation shall vest its general management in a Board of Regents and in a Board of Governors as hereinafter provided.

Article IV

Membership

Members of the College shall be of four classes:

(a) Masters. Masters of the American College of Physicians shall have been Fellows who, on account of personal character, positions of honor and influence, eminence in practice or in medical research, or other attainments in science or in the art of medicine, are recommended by the Committee on Masterships and Honorary Fellowships to the Board of Regents and who are elected by the Board of Regents. Masters shall be designated as Masters of the American College of Physicians, and shall be authorized to use the letters M.A.C.P. in connection with scientific publications, at professional and academic functions and in connection with their professional activities.

Masters shall have the right to vote and to hold office.

(b) Fellows. Fellows shall be members of the medical profession engaged as practitioners, teachers or research workers in Internal Medicine, or in an allied specialty, who shall have been elected in accordance with the By-Laws and such additional rules as the Board of Regents may from time to time adopt.

Fellows shall be authorized to use the letters F.A.C.P. in connection with scientific publications, at professional and academic functions and in connection with their professional activities.

Fellows shall have the right to vote and to hold office.

(c) Honorary Fellows. Honorary Fellows, except as noted in the following paragraph, shall be members of the medical profession of countries other than the United States, Canada, Cuba, Mexico, or the Central American Republics, who on account of personal character, positions of honor and influence, or eminence in Internal Medicine, or an allied specialty, shall be recommended by the Committee on Masterships and Honorary Fellowships to the Board of Regents and who are elected by the Board of Regents.

In exceptional instances, and then only by reason of outstanding service to Internal Medicine, the Committee on Masterships and Honorary Fellowships may recommend to the Board of Regents for election to Honorary Fellowship others than members of the medical profession, regardless of their nationality or residence.

Honorary Fellows shall not have the right to vote or to hold office.

(d) Associates. Associates shall be members of the medical profession engaged as practitioners, teachers or research workers in Internal Medicine, or in an allied

specialty, who shall have been elected in accordance with the By-Laws and such additional rules as the Board of Regents may from time to time adopt, the By-Laws and additional rules being intended to insure the election to Associateship only of persons whose qualifications are such as to give promise of subsequent development within the time specified in the By-Laws, as would entitle them to election to Fellowship. It is intended that Associateship shall be in effect a probationary status from which the holder may be elevated to Fellowship, within a specified period of time, upon presenting the evidence of possessing the qualifications required for election to Fellowship.

Associates shall receive all scientific publications of the College and may participate in the Annual Session and Regional Meetings of the College, but they shall not have the right to vote or to hold office.

Article V

Constitutional Committees

The Constitutional Committees shall be: (a) Executive Committee of the Board of Regents; (b) Executive Committee of the Board of Governors; (c) Committee on Credentials; (d) Committee on Educational Program; (e) Committee on Finance and Budgets; (f) Committee on Masterships and Honorary Fellowships; (g) Committee on Awards, and (h) Committee on Nominations. The membership and functions of these Committees shall be as stated in the By-Laws.

Article VI

Amendments

Proposed amendments to this Constitution shall first be submitted to the Board of Regents for its recommendation. The recommendation of the Board of Regents shall then be presented to the Masters and Fellows of the College for their consideration at least thirty days before the annual business meeting, either through the official publications of the College or by letter.

A two-thirds vote of the Masters and Fellows voting at an annual business meeting shall be necessary to adopt an amendment.

BY-LAWS

Article I

Officers

Section 1. The Officers of the College shall be a President, a President-Elect, a First Vice President, a Second Vice President, a Third Vice President, a Secretary-General, and a Treasurer.

Section 2. The President-Elect, the First Vice President, the Second Vice President and the Third Vice President shall be elected at the annual business meeting of the College, each for a term of one year or until his successor is elected. The President-Elect shall enter upon his duties as President at the annual business meeting following his election. The Secretary-General and the Treasurer shall be elected by the Board of Regents for terms of three years and shall be eligible for re-election for three additional terms.

Section 3. The President of the College shall preside at all regular and special meetings of the College, of the Board of Regents and of the Executive Committee, and

at all convocations for the conferring of certificates of Master, Fellow, and Honorary Fellow. He shall be a voting member of all standing committees of the Board of Regents, except the Committee on Masterships and Honorary Fellowships, the Committee on Awards and the Committee on Nominations.

Section 4. The President-Elect shall be an ex officio member of all standing committees of the Board of Regents, except the Committee on Masterships and Honorary Fellowships, the Committee on Awards and the Committee on Nominations.

Section 5. The First Vice President shall assume the duties of the President in the event of the death, resignation, or absence of the President.

Section 6. The Second Vice President shall assume the duties of the First Vice President in the event of the death, resignation, or absence of the First Vice President.

Section 7. The Third Vice President shall assume the duties of the Second Vice President in the event of the death, resignation, or absence of the Second Vice President.

Section 8. The Secretary-General shall be Secretary of the corporation and shall sign certificates and all official documents. He shall be Chairman of the Committee on Credentials and an ex officio member of all other standing committees, except the Committee on Masterships and Honorary Fellowships, the Committee on Awards and the Committee on Nominations.

Section 9. The Treasurer shall receive all funds of the College and disburse the same by cheque, signed by him, upon voucher signed by the Executive Secretary. He shall make a report in writing to the Board of Regents of the moneys received and expended, furnishing a detailed statement of the financial condition of the College at each Annual Business Meeting. He shall furnish a bond to the Board of Regents in such sum as may be designated by the Board of Regents for the faithful performance of his trust, premium upon same to be paid by the College.

Section 10. The Board of Regents shall appoint a Chief Administrative Officer with such assistants as the Board may deem advisable and by whatever title or titles the Board may designate. Under the direction of the Board of Regents, the Chief Administrative Officer shall have supervision of the activities and business affairs of the College. The Chief Administrative Officer, or a designated assistant, shall: (1) act as Secretary to the Board of Regents, the Executive Committee of the Board of Regents, and the Board of Governors; (2) direct the executive offices of the College, maintaining all records such as those of membership, inventories and accounting; (3) collect initiation fees and dues; (4) prepare a budget covering all expenditures for the organization, said budget to be approved by the Committee on Finance and Budgets and by the Board of Regents or the Executive Committee; (5) issue all vouchers for payment of bills on budget authorizations; (6) assist in the auditing of the Treasurer's accounts; (7) mail notices, announcements, et cetera, of all regular or special meetings of the College to all members of record; (8) under the direction of the Board of Regents provide for Convocations and Annual Sessions; (9) perform such other duties as are assigned to him by the Board of Regents; and (10) report to the Board of Regents at its regular sessions or whenever requested by the Board.

The administrative officers shall be bonded in such sum as may be designated and determined by the Board of Regents, premium for same to be paid by the College.

Article II

Board of Regents

Section 1. The Board of Regents shall consist of the President, the President-Elect, the three immediately preceding past Presidents, the Vice Presidents, the Secretary-General, the Treasurer, the Chairman of the Board of Governors, and

fifteen members elected from among the Masters and Fellows at the Annual Business Meeting of the College. A past President shall serve one term of three years as Regent, and shall not be eligible for re-election. The Editor of the official journal shall be an ex officio member of the Board of Regents.

Section 2. The elected members of the Board of Regents shall each serve for a term of three years, and for not more than three consecutive terms, exclusive of any unexpired fraction of a term previously served.

Section 3. The duties of the Board of Regents shall be those ordinarily performed by a board of directors of a corporation, namely: to transact all detail business required to carry out the objects of the organization; to regulate and to conserve the property interests of the College; to approve or disapprove the recommendations of the Committee on Finance and Budgets and to be responsible for all expenditures of the College; to fix initiation fees and annual dues of members; to adopt, from time to time, rules and regulations for the election of Masters, Fellows, Honorary Fellows, and Associates supplementary to the regulations contained in the By-Laws: to create, appoint and direct all standing committees; to create, appoint and direct special committees as the Board of Regents finds necessary for the conduct of the affairs of the College; to elect editors and committees on publications for all publications of the organization; to call all meetings of the corporation not already provided for; to make arrangements through the Administrative Staff for Convocations, the Annual Session, and other meetings; to elect Masters, Fellows, Honorary Fellows, and Associates; and to transact all business not otherwise provided for that may pertain to the organization.

Section 4. Nine members of the Board of Regents shall constitute a quorum for the transaction of business.

Section 5. Regular meetings of the Board of Regents shall be held at least twice annually at the call of the President, at the time and place of the Annual Session and in the autumn. Special meetings may be convened at any time by the President, or on a request made in writing and signed by fifteen members of the Board of Governors, or by twelve members of the Board of Regents.

Section 6. No elected officer or elected member of the Board of Regents shall be a member of the Board of Governors at the same time.

Section 7. In the event of death or resignation of any member of the Board of Regents, his successor shall be elected at the next regular business meeting of the College, but the Board of Regents may appoint a Master or Fellow to serve as Regent until this election shall have taken place.

Article III

Constitutional Committees of the Board of Regents

Section 1. *Executive Committee.*

Membership: The Board of Regents shall elect annually three of its members, nominated by the President; these, together with the President, President-Elect, Secretary-General, Treasurer, Chairman of the Board of Governors, and Chairman of the Committee on Finance and Budgets, shall constitute an Executive Committee. Members of the Executive Committee shall be eligible for re-election.

Functions: The functions of the Executive Committee shall be: (1) during the intervals between the meetings of the Board of Regents to exercise all the powers of the Board of Regents in the management and direction of the business and the conduct of the affairs of the corporation; except that it shall not have the power to elect Masters, Fellows, Honorary Fellows, or Associates, or to regulate initiation fees or annual dues; (2) to keep a record of its proceedings and report the same to the Board of Regents at the next succeeding meeting for its approval; (3) at its

discretion, to appoint such subcommittees as it may deem necessary or desirable for the proper transaction of the business of the corporation; (4) to adopt rules and regulations for the conduct of its meetings and activities, not inconsistent with the Constitution and By-Laws of the College and the Laws of the State under which the College is incorporated; and (5) to hold its meetings at such place or places as it may from time to time determine, a majority of the Executive Committee constituting a quorum for the transaction of business.

Meetings: Meetings of the Executive Committee may be called by the President or by any three members of the Committee.

Section 2. *Committee on Credentials.*

Membership: The Committee on Credentials shall consist of seven members, three to be Regents at the time of appointment and elected by the Board of Regents on nomination of the President, three to be Governors at the time of appointment and to be elected by the Board of Governors on nomination of its Chairman, and the Secretary-General, who shall serve as Chairman. The term of office for Regents and Governors shall be three years with eligibility for reappointment, provided the Fellow is still a member of the Board of Regents or Board of Governors at the time of reappointment; not more than one new member shall be appointed from each Board each year (except in case of death or resignation). The Chairman of the Committee, with the approval of the President, may appoint temporary members as needed for any meeting of the Committee.

Functions: The functions of the Committee on Credentials shall be: (1) to pass upon the qualifications of physicians proposed for Fellowship or Associateship in the College as provided in the By-Laws and to recommend those considered eligible to the Board of Regents, and (2) to recommend to the Board of Regents changes in criteria for selection of candidates which in its experience the Committee believes to be in the best interests of the College.

Section 3. *Committee on Educational Program.*

Membership: The Committee on Educational Program shall consist of five Regents, one to be the Chairman of the Board of Governors. The Chairman of the Committee shall be designated by the President. The Committee shall be appointed by the Board of Regents on nomination by the President. Members shall serve for three years and shall be eligible for reappointment while still serving on the Board of Regents.

Functions: The functions of the Committee on Educational Program shall be: (1) to study and consider in their broadest aspects all educational functions of the College, including the Annual Sessions, Postgraduate Courses, Regional Meetings, fellowship programs, the Annals of Internal Medicine, and any other publications of the College; to recommend to the Board of Regents educational policies which will render most effective all educational functions of the College; (2) to serve as a channel of communication to the Board of Regents for, and co-ordinate the activities of, those committees which deal with specific aspects of the educational program.

Section 4. *Committee on Finance and Budgets.*

Membership: The Committee on Finance and Budgets shall consist of three Regents, each serving for a term of three years, the terms so arranged that one will expire each year. Members shall be eligible for reappointment as long as they are Regents. The President shall nominate annually to the Board of Regents the new member (or members in case of death or resignation) and designate the Chairman. The President, President-Elect, and Treasurer shall also be voting members.

Functions: The functions of the Committee on Finance and Budgets shall be: (1) to report to the Board of Regents at each meeting regarding the financial affairs, assets and liabilities of the College; (2) to review and to make recommendations

concerning proposed expenditures for the next succeeding calendar or fiscal year; (3) to review and submit the proposed budget of the College to the Board of Regents at its autumn meeting; and (4) to make recommendations regarding fiscal policy to the Board of Regents.

Section 5. *Committee on Masterships and Honorary Fellowships.*

Membership: The Committee on Masterships and Honorary Fellowships shall consist of two Regents and one Governor, appointed for a term of three years by the Board of Regents on nomination by the President so that one member shall retire each year. Members shall be eligible for reappointment once if still a member of the Board of Regents or Board of Governors. The Chairman, a Regent, shall be designated annually by the President. It shall be the duty of the Chairman, or of some member of the Committee appointed by the Chairman, to be in liaison with the Committee on Awards so that no individual shall be nominated at the same time for an Award and a Mastership in the College.

Function: The Committee shall bring its nominations for Masters and Honorary Fellows to the Board of Regents for approval or rejection.

Section 6. *Committee on Awards.*

Membership: The Committee on Awards shall consist of three Regents and two Governors appointed for staggered terms of three years by the Board of Regents on nomination by the President, and shall not be eligible for reappointment. The Chairman, a Regent, and when necessary a Vice Chairman, also a Regent, shall be appointed by the President. It shall be the duty of the Chairman, or of some member of the Committee appointed by the Chairman, to be in liaison with the Committee on Masterships and Honorary Fellowships so that no individual shall be nominated at the same time for an Award and a Mastership in the College.

Functions: The Committee shall bring its nominations for the various Awards of the College, including the John Phillips Memorial Award, the James D. Bruce Memorial Award, the Alfred Stengel Memorial Award, and the American College of Physicians Award, to the Board of Regents for approval or rejection.

Section 7. *Committee on Nominations.*

Membership: The Committee on Nominations shall consist of two Regents, two Governors and one Fellow-at-Large, appointed by the President within one month after induction to office. The Chairman, a Regent, shall be designated by the President. One member shall be reappointed for one year, but no member for more than two years in succession.

Functions: The functions of the Committee on Nominations shall be: (1) to nominate candidates for the elective offices, Board of Regents and Board of Governors, the selection of nominees for the Board of Governors to be made after due consideration of suggestions of members from the jurisdictional areas and governmental services to be represented; and (2) to submit to all the Masters and Fellows of the College at least one month prior to the annual business meeting the list of nominees for President-Elect and First, Second and Third Vice Presidents.

ARTICLE IV

Board of Governors

Section 1. At the annual business meeting of the College, the Masters and Fellows in open session shall elect certain of their members to serve on the Board of Governors, to represent jurisdictional areas and governmental services as determined from time to time by the Board of Regents and approved by the College at the annual business meeting.

Section 2. The term of service of a Governor shall be three years. The term of one-third of the Governors shall expire each year and not more than three consecutive terms shall be served, exclusive of any unexpired fraction of a term previously served. The terms of additional Governors shall be regulated so as to retain equal distribution and rotation in each group.

Section 3. The President shall fill all vacancies in the current membership of the Board of Governors due to death, resignation or other cause, until such time as successors shall have been elected in the regular manner.

Section 4. Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow from his jurisdiction to represent him. Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed. The same alternate shall not be appointed for more than two consecutive years.

Section 5. The Board of Governors shall meet annually at the time and place of the Annual Session of the College for the transaction of such business as may come before it. Special meetings shall be called by the Chairman, or on the petition of the Board of Regents, or on the petition of fifteen members of the Board of Governors.

Section 6. The Board of Governors shall elect a Chairman and a Vice Chairman, who shall serve for terms of three years each, unless their membership on the Board of Governors expires before the end of three years. In the event of vacancy of the Chairmanship, the Vice Chairman shall act as Chairman until the next meeting of the Board of Governors at which time a Chairman shall be elected by the Board of Governors to serve the unexpired term. In the event of vacancy of the offices of both Chairman and Vice Chairman of the Board of Governors, the Executive Committee of this body shall appoint one of its members to serve as Chairman of the Board of Governors until the next meeting of the Board of Governors.

Section 7. The Chairman of the Board of Governors shall be a member of the Board of Regents. With the exception of the Chairman of the Board of Governors, no Governor shall be a member of the Board of Regents at the same time.

Section 8. The Board of Governors, on nomination of its Chairman, shall appoint three members to serve on the Committee on Credentials.

Section 9. Twenty members of the Board of Governors shall constitute a quorum for the transaction of business. Voting by proxy shall not be allowed.

Article V

Committees of the Board of Governors

Section 1. *Executive Committee.*

Membership: The Executive Committee of the Board of Governors shall consist of eight Governors, including the Chairman and Vice Chairman who shall serve as Chairman and Vice Chairman of the Executive Committee. The six other members shall be elected by the Board in such a manner that two members shall retire each year.

Functions: The functions of the Executive Committee of the Board of Governors shall be: (1) during the intervals between meetings of the Board of Governors, to exercise all the powers of the Board of Governors in the management and direction of its business and the conduct of its affairs; (2) to keep a record of its proceedings and report the same to the Board of Governors at the next succeeding meeting for its approval; (3) at its discretion to appoint such sub-committees as it may deem necessary or desirable; (4) to hold its meetings at such place or places as it may

from time to time determine; (5) a majority of the Executive Committee shall constitute a quorum for the transaction of business.

Section 2. *Committee on Postgraduate Courses.*

Membership: The Committee on Postgraduate Courses shall consist of six Governors appointed by the Chairman of the Board of Governors who shall designate one of the members to serve as Chairman of the Committee. They shall be appointed in such a manner that the terms of two members shall expire each year.

Function: This Committee shall have full charge of, and thereby be responsible for, all Postgraduate Courses sponsored by the College and, through the Chairman, shall report to the Board of Governors and the Board of Regents.

Section 3. *Nominating Committee.*

Membership: The Nominating Committee of the Board of Governors shall consist of three members appointed by the Chairman.

Function: The Nominating Committee of the Board of Governors shall offer at the annual meeting of the Board of Governors, nominations for Chairman, Vice Chairman and members of the Executive Committee of the Board of Governors.

Article VI

Qualifications for Fellowship

Section 1. A Fellow of the College shall have met the following qualifications and requirements:

(a) He shall have qualified and served a minimum period of three years as an Associate, except upon recommendation of the Committee on Credentials by reason of very special qualifications as hereinafter set forth.

(b) He shall have been graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and, if engaged in practice, his professional activity must be confined to Internal Medicine or an allied specialty.

(c) If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of Internal Medicine or an allied specialty at a permanent location for at least three years preceding nomination for Fellowship.

(d) The criteria of eligibility for election to Fellowship are:

1. Detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions, a thesis, or five case reports of personal cases thoroughly documented and discussed, prepared during Associateship, and acceptable to the Committee on Credentials; personal approval by Masters, Fellows and the Governor in the jurisdiction of the candidate, with reference to his character, ethical standing and medical activities; evidence of postgraduate training and attendance upon the Annual Sessions of the College.
2. He shall be certified by the recognized national board of certification in his particular field, where such an accrediting board exists.

(e) The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify these regulations in exceptional cases.

Proposal for Fellowship

Section 2. The name of the candidate shall be proposed to the Officers and Board of Regents on the official blank of the College by a Master or Fellow of the

College neither of whom shall be an Officer, Regent or Governor of the College. The proposer and seconder shall be from the Governor's jurisdiction in which the candidate practices or serves. However, in exceptional cases, when the candidate practices near another Governor's jurisdiction where he is better known, the proposer, the seconder, or both, may be residents of that jurisdiction and not the one in which the candidate practices. The proposal must be endorsed by the Governor in the jurisdiction in which the candidate practices or serves, or, in special instances, by his designated representative. The proposal must be accompanied by adequate written statements made both by the proposer and the seconder, setting forth all of the above described qualifications of the candidate. The proposer must be prepared to add such further information as may be requested by the Committee on Credentials. The name of the candidate shall be sent to each Master and Fellow in the candidate's locality in order that he may have the opportunity to communicate to the Committee on Credentials any favorable or unfavorable information about the candidate.

Election of Fellows

Section 3. The credentials of a candidate for Fellowship shall be considered first by the Committee on Credentials, which shall report the candidate to the Board of Regents for election or rejection.

Section 4. A successful candidate shall receive at once, from the Board of Regents through the Chief Administrative Officer, an appropriate official notification of his election to Fellowship in the College and shall be urged to attend the next succeeding Convocation, when Fellowships will be formally conferred. The official Fellowship Certificate, signed by the President and the Secretary-General, shall be issued following the Convocation. Acknowledgment of its receipt shall be made upon an official card, signed and dated by the newly elected Fellow.

Section 5. Proposal for direct election to Fellowship, with or without prior certification by the appropriate certifying board, and regardless of preceding status as an Associate, may be made to the Committee on Credentials. This manner of election is an unusual mark of distinction; hence such candidates must be preëminent in teaching, research or clinical practice. In the proposal of individuals for such consideration, the following details must be furthermore considered: maturity, national reputation, publications, and other contributions to medical science and public welfare.

This ruling will be invoked for candidates who have failed for regular advancement from Associateship to Fellowship at the discretion of the Committee on Credentials only in the case of candidates of unusual distinction.

ARTICLE VII

Election of Masters and Honorary Fellows

Masters and Honorary Fellows shall be elected by the Board of Regents upon recommendation of the Committee on Masterships and Honorary Fellowships.

ARTICLE VIII

Qualifications for Associateship

Section 1. An Associate of the College shall have met the following qualifications and requirements:

(a) He shall hold the degree of M.D., M.B., or M.D., C.M., acceptable to the Board of Regents.

(b) After receiving his medical degree the candidate shall have had at least one year of internship and three years of organized graduate training in Internal Medicine or allied fields, or its equivalent, acceptable to the Board of Regents. One year of this graduate training may be spent in the basic sciences.

(c) If a practitioner, he shall be duly licensed to practice medicine and shall indicate his purpose to confine his practice to Internal Medicine or an allied specialty from the date of his application. If not a practitioner, he shall hold an official institutional position in Internal Medicine, an allied branch of Internal Medicine, or in medical research, or be in active governmental service.

Proposal for Associateship

Section 2. The name of the candidate shall be proposed to the Officers and Board of Regents on the official blank of the College by a Master or Fellow of the College neither of whom shall be an Officer, Regent or Governor of the College. The proposer and seconder shall be from the Governor's jurisdiction in which the candidate practices or serves. However, in exceptional cases, when the candidate practices near another Governor's jurisdiction where he is better known, the proposer, the seconder, or both, may be residents of that jurisdiction and not the one in which the candidate practices. The proposal must be endorsed by the Governor in the jurisdiction in which the candidate practices or serves, or, in special instances, by his designated representative. The proposal must be accompanied by adequate written statements made both by the proposer and the seconder, describing all of the above qualifications of the candidate. The proposer must be prepared to add such further information as may be requested by the Committee on Credentials. The name of the candidate shall be sent to each Master and Fellow in the candidate's locality in order that he may have the opportunity to communicate to the Committee on Credentials any favorable or unfavorable information about the candidate.

Election of Associates

Section 3. The credentials of a candidate for Associateship shall be considered first by the Committee on Credentials, which Committee shall report the candidate to the Board of Regents for election or rejection.

Section 4. A successful candidate shall receive at once, from the Board of Regents through the Chief Administrative Officer, an appropriate official notification of his election.

Term of Associateship and Eligibility for Fellowship

Section 5. An Associate shall be eligible for election to Fellowship at the end of three years. Upon expiration of this three-year period, he shall be notified in writing by the Committee on Credentials of his eligibility for proposal for advancement to Fellowship. If he is not elected to Fellowship within a total of ten years, his Associateship shall automatically terminate. Upon recommendation by the Governor, the Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions.

If Associateship has been terminated as herein provided but the individual subsequently becomes able to fulfill all requirements for advancement to Fellowship to the complete satisfaction of the Committee on Credentials, he may be reproposed to the Committee on Credentials, which body may recommend to the Board of Regents his reinstatement as an Associate and his immediate advancement to Fellowship.

Article IX

Fees and Dues

The Board of Regents shall establish initiation fees, annual dues, and Life Membership fees.

The annual dues or the Life Membership fee shall entitle each Master, Fellow and Associate to privileges of membership of his respective class, to the benefits of the Annual Sessions and to the scientific publications of the College. An Honorary Fellow shall not pay dues but shall have the privilege of attending all scientific meetings.

A Master, Fellow or Associate of the College shall not be required to pay dues after attaining the age of 65 years, or after he has submitted satisfactory evidence to the Board of Regents to show that he has retired from the active practice of medicine or from scientific medical research.

At the discretion of the Board of Regents, without publicity, initiation fees or annual dues may be remitted, in whole or in part, as in case of a member engaged in purely scientific research, full-time medical teaching, active government service, or in the case of any member suffering serious disability or financial reverses. In case of change of status to private practice or similarly remunerative occupation, the Board of Regents may require the payment of the usual annual dues.

Article X

Endowment Fund

It shall be the duty of the Board of Regents to provide a plan for securing an adequate endowment, the principal of which shall be held intact and invested in securities approved by the Board of Regents, while the income shall be available for carrying out the purposes of the organization. Such endowment fund shall consist of: (1) all moneys received for Life Membership in the College; (2) such moneys as may be set aside by the Board of Regents from time to time from the funds of the College, and (3) such moneys as may be donated directly to the fund.

Article XI

Publications

Section 1. The Board of Regents shall issue from time to time a Directory of the College, containing the names, addresses and pertinent information of the Masters, Fellows, Honorary Fellows and Associates.

Section 2. The Board of Regents shall publish a journal devoted to the advancement of Internal Medicine. Other publications may be authorized by the Board of Regents.

Section 3. The Board of Regents shall appoint editors and editorial boards to carry out these provisions.

Article XII

Annual Business Meeting

A business meeting of the College shall be held each year, during the week of the Annual Session, for the election of Officers, Regents and Governors, and for the transaction of such other business as may be necessary. In addition to the nominations of the Nominating Committee, nominations for Officers, Regents and Governors may be made from the floor.

Article XIII

Annual Convocation

The College shall hold an annual Convocation for the induction of newly elected Fellows, for the conferral of the certificate of "Master," "Fellow," and "Honorary Fellow," and for the presentation of official awards. A Presidential address shall be delivered on, or before, this occasion.

Article XIV

Annual Session

Section 1. The College shall conduct annually a scientific session devoted to subjects of importance to those interested in Internal Medicine and its branches. The Annual Session is intended primarily for the benefit of the Masters, Fellows and Associates of the College, but physicians and other scientists who are not members may attend as guests, upon invitation by the Board of Regents.

Section 2. The Board of Regents shall be responsible for the conduct of the Annual Session. It shall provide a General Chairman who shall appoint suitable committees to organize and conduct the Session under the direction of the Board of Regents and the President.

Section 3. The Chief Administrative Officer and his staff, acting under the direction of the Board of Regents, shall make all necessary arrangements for the Annual Session.

Article XV

Discipline

Section 1. Any Master, Fellow or Associate of the College may be disciplined or expelled for conduct which, in the opinion of the Board of Regents, is derogatory to the dignity of the College or inconsistent with its purposes. Expulsion shall require a two-thirds vote of the Board of Regents at a meeting at which the Master, Fellow or Associate against whom charges are preferred shall be requested to be present. In case such Master, Fellow or Associate does not appear, he may be represented in a manner to be determined by the Board of Regents.

Section 2. A Master, Fellow or Associate who is delinquent in dues automatically loses all privileges of his membership. After two years' delinquency, and notification by the Board of Regents, he shall be dropped from the roll of the College.

Article XVI

Amendments

These By-Laws may be amended by the unanimous vote of those present at any Annual Business Meeting of the College, or by a majority vote if notice of such amendment has previously been submitted in writing to the Board of Regents and presented to the Masters and Fellows of the College at least thirty days before the time of such meeting, either through official publications of the College or by letter.

In accordance with provisions of the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1959–60, are herewith announced to the Fellows and Masters of the College:

President-Elect .....Chester S. Keefer, Boston, Mass.
First Vice President .....Wesley W. Spink, Minneapolis, Minn.
Second Vice President .....Walter de M. Scriver, Montreal, Que.
Third Vice President .....Garfield G. Duncan, Philadelphia, Pa.

Regular elections will take place at the 1959 Annual Session, Chicago, Ill., on April 23, 1959, 1:45 P.M., the date of the Annual Business Meeting, at the Conrad Hilton Hotel.

Election of nominees shall be by the Fellows and Masters. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations of members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,

J. Murray Kinsman, Chairman, Louisville, Ky.
Howard Wakefield, Chicago, Ill.
Theodore C. Bauerlein, Salt Lake City, Utah
Percy H. Sprague, Edmonton, Alta., Canada
Worth B. Daniels, Washington, D. C.

NEW LIFE MEMBER

The College acknowledges with pleasure the following Fellow as a new Life Member:

Dr. Fred R. Sloan, Waterloo, Iowa

The College gratefully acknowledges receipt of the following books from members of the College to the Memorial Library of Publications by Members of the College:

E. Grey Dimond, M.D., F.A.C.P., Kansas City, Kans., ELECTROCARDIOGRAPHY (2nd edition), printed by Fine Arts Lithographing Co., Inc., Kansas City, Mo., 1957, 172 pages.

Robert S. Dow, M.D., F.A.C.P., Portland, Ore., THE PHYSIOLOGY AND PATHOLOGY OF THE CEREBELLUM, published by The University of Minnesota Press, Minneapolis, Minn., 1958, 675 pages.

William Carleton Gibson, M.D., F.A.C.P., Vancouver, B.C., Can., YOUNG ENDEAVOUR, published by Charles C Thomas, Publisher, Springfield, Ill., 1958, 292 pages.

Tinsley R. Harrison, M.D., F.A.C.P., Birmingham, Ala., PRINCIPLES OF INTERNAL MEDICINE (third edition), published by McGraw-Hill Book Company, New York, Toronto and London, 1958, 1,782 pages.

Hans H. Hecht, M.D., F.A.C.P., Salt Lake City, Utah, THE ELECTROPHYSIOLOGY OF THE HEART, published by the New York Academy of Sciences, 1957, Volume 65, Article 6, Pages 653–1146, of the *Annals of the New York Academy of Sciences.*

Fred B. Rogers, M.D., (Associate), Philadelphia, Pa., A SYLLABUS OF MEDICAL HISTORY, printed by Stephenson-Brothers, Philadelphia, 1958, 26 pages.

David A. Rytand, M.D., F.A.C.P., San Francisco, Calif., ANNUAL REVIEW OF MEDICINE, published by Annual Reviews, Inc., Palo Alto, Calif., 1958, 530 pages.

Alexander S. Wiener, M.D., F.A.C.P., Brooklyn, N. Y., HEREDITY OF THE BLOOD GROUPS, published by Grune & Stratton, New York and London, 1958, 150 pages.

A.C.P. Regional Meetings

The following regional meetings have been held during the past six months: North Dakota, September 6; Michigan, September 19–20; Idaho-Utah, September 27; Midwest (Ill., Ind., Iowa, Minn., Wis.), September 27; Western New York, October 3; Southeastern (Ala., Fla., Ga., Miss., S.C., Cuba), October 3–4; Montana-Wyoming, October 10–11; Arizona, October 18; Arkansas-Oklahoma, October 18; Kentucky-Tennessee, October 18; District of Columbia-Maryland-Delaware, November 1; New England-Quebec-Atlantic Provinces, November 7–8; New Jersey, November 12; North Carolina, December 4; Puerto Rico, December 19–20; Colorado, January 16–17; Ohio, January 22; Eastern Pennsylvania, January 23; Alberta-Manitoba-Saskatchewan, January 29; Southern California, February 7–8; Pacific Northwest (British Columbia, Ore., Wash.), February 14; Louisiana-Mississippi, February 20, and Missouri, February 21.

The following meetings are yet to be held:

Territory	City	Date	Governor(s)	Official Guest(s)
Nebraska	Omaha	March 7, 1959	Edmond M. Walsh	Dwight L. Wilbur, Pres.
Kansas	Wichita	March 20, 1959	Fred J. McEwen	
Virginia	Hot Springs	March 21, 1959	Charles M. Caravati	Dwight L. Wilbur, Pres.

Recent Meetings in Hawaii

Dr. Arthur V. H. Molyneux, F.A.C.P., Honolulu, T.H., reports that the Hawaii Chapter of the College held one of its periodic dinner meetings at the Pacific Club in Honolulu on November 3, 1958. It was attended by members of the local group, military service members and guests. Dr. Louis E. Martin, Sr., F.A.C.P., Los Angeles, Calif., the Guest of Honor, spent the evening discussing questions presented by others in round table discussion.

This meeting followed the first Special Cardiology Sessions of the Hawaii Heart Association, held October 31 and November 1 at the Princess Kaiulani Hotel, in Honolulu. The session was attended by several visiting physicians, many of whom are College members, who had been at the American Heart Association meeting in San Francisco.

Among those participating in the Honolulu meetings were Dr. Louis E. Martin, Sr., F.A.C.P., Los Angeles, Calif.; Dr. Robert W. Wilkins, F.A.C.P., Boston, Mass., and immediate Past President of the American Heart Association; Dr. E. Cowles Andrus, F.A.C.P., The Johns Hopkins University School of Medicine, Baltimore, Md., and Dr. Herbert Pollack, F.A.C.P., Associate Professor of Clinical Medicine, New York University Post-Graduate Medical School, New York, N. Y.

Dr. Fred I. Gilbert, Jr., F.A.C.P., Honolulu, President of the H.H.A., was Chairman for the first day's meetings, and Dr. Morton E. Berk, F.A.C.P., Honolulu, Past President of the H.H.A., was Chairman of the second day's sessions. A panel on "Rheumatic Fever" consisted of: Dr. Coolidge W. Wakai, Honolulu, Moderator; Dr. Louis E. Martin, Jr., F.A.C.P., Los Angeles, Calif.; Dr. Albert H. Ishii, (Associate), Honolulu; Dr. Chew Mung Lum, (Associate), Honolulu, and Dr. Scott B. Brainard. Another panel on "Hypertension" included: Dr. Bernard W. Fong, Moderator; Dr. E. Cowles Andrus, F.A.C.P., Baltimore, Md.; Dr. Robert W. Wilkins, F.A.C.P., Boston, Mass., and Dr. George H. Mills. A third panel on "Atherosclerosis in Hawaii" was composed of: Dr. Kikuo Kuramoto, Moderator; Dr. Herbert Pollack, F.A.C.P., New York, N. Y.; Dr. Nils P. Larsen, F.A.C.P., Honolulu, former A.C.P. Governor for Hawaii, and Dr. Leo H. T. Bernstein, (Associate), Martinsburg, W. Va.

Dr. Bernard J. B. Yim, Honolulu, presented a paper on the subject, "The Diagnosis of Ebstein's Disease with the Aid of the Electrode Catheter," in the absence of Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., who was unable to attend.

A cardiac clinic was presented at the Queen's Hospital under the direction of Dr. Henry C. Gotshalk, F.A.C.P., Honolulu, Chief of the Medical Staff.

Graduate Fellowships in Industrial Medicine

Graduate Fellowships in Industrial Medicine are available at the Institute of Industrial Health, University of Cincinnati College of Medicine, to graduates of approved medical schools who have completed at least one year of internship. Annual stipends will range from $3,000 to $4,000 for the first two years which are devoted to academic and clinical study in the field of industrial medicine. The final year spent in residency in an industrial medical department or a comparable organization, will be financed by the institution. The three-year course of instruction which meets the requirements for certification in occupational medicine by the American Board of Preventive Medicine, will lead to the degree of Doctor of Science in Industrial Medicine. For further information, write the Secretary, Institute of Industrial Health, College of Medicine, Eden and Bethesda Aves., Cincinnati 19, Ohio.

Physical Medicine and Rehabilitation Essay Awards

The American Congress of Physical Medicine and Rehabilitation announces its 6th Annual Essay Award of $200 and the Bernard M. Baruch Award of $100 for essays on subjects related to physical medicine and rehabilitation. The first award will be available to interns, residents, graduate students in the pre-clinical sciences and graduate students in physical medicine and rehabilitation, while the Bernard M. Baruch Essay Award will be available to medical students only. Essays should not exceed 3000 words, exclusive of references, headings and tables. Duplicate copies must be submitted not later than March 2, 1959. For information write Dorothea C. Augustin, Executive Secretary, American Congress of Physical Medicine and Rehabilitation, 30 N. Michigan Ave., Chicago 2, Ill.

American Board of Pediatrics

The American Board of Pediatrics has announced the following list of oral examinations to be scheduled in 1959. They are: New Orleans, La., March 6, 7, 8; Philadelphia, Pa., May 3, 4, 5; San Francisco, Calif., June 19, 20, 21; Chicago, Ill., October 9, 10, 11, and Washington, D. C., December 4, 5, 6.

The following rules govern the selection of candidates: 1. Candidates must have passed a written examination. 2. Candidates will be called in the order in which their applications were received. Since only a predetermined number can be examined orally in a given year, those enrolled for the written examination who are in excess of that number will be designated as "alternates." They may be called to fill vacancies that develop or may not be called until 1960. 3. Candidates will not be called far in advance of their eligibility date, and should not choose a date more than one month prior to the same. 4. Candidates should make a second choice, as the list for each session must be filled. "Alternates" should also list a first and second choice and, so far as possible, these will be heeded. 5. All candidates for oral examination in 1959 should make their choices NOW and not wait to learn the results of written examinations. Write to The American Board of Pediatrics, Inc., 6 Cushman Rd., Rosemont, Pa.

7th Postgraduate Course of the American Diabetes Association

The 7th Postgraduate Course on Diabetes and Basal Metabolic Problems jointly sponsored by the American Diabetes Association, the St. Louis University School of Medicine, the Washington University School of Medicine, and the University of Missouri School of Medicine, was held in St. Louis, Mo., January 22–23, 1959. Fifteen members of the College participated as members of the faculty. Fellows of the College included the following: Drs. Frank N. Allan, Boston, Mass.; Arthur R. Colwell, Sr., Chicago, Ill.; Jerome W. Conn, Ann Arbor, Mich.; Garfield G. Duncan, Philadelphia, Pa.; T. S. Danowski, Pittsburgh, Pa.; Franklin B. Peck, Sr., Indianapolis, Ind.; Robert M. Kark, Chicago, Ill.; John A. Reed, Washington, D. C.; Alexander Marble, Chestnut Hill, Mass.; Thomas P. Sharkey, Dayton, Ohio; E. Paul Sheridan, Denver, Colo., and Henry T. Ricketts, Chicago, Ill. The Associates included: Drs. Thomas W. Burns, Columbia, Mo.; Harvey C. Knowles, Jr., Cincinnati, Ohio, and Theodore B. Van Itallie, New York, N. Y.

Postgraduate Course on Diseases of the Chest

The American College of Chest Physicians announces that its Council on Postgraduate Medical Education will present the 12th Annual Postgraduate Course on Diseases of the Chest at the Sheraton Hotel, Philadelphia, Pa., March 30–April 3, 1959. The most recent advances in the diagnosis and treatment of heart and lung diseases will be presented. Tuition for the five-day course will be $100. For information write the Executive Director, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill.

Meeting of the Pennsylvania Society of Internal Medicine

Dr. George L. Jackson, (Associate), Harrisburg, Pa., President of the Pennsylvania Society of Internal Medicine, presided at the annual Meeting of the Society held in Philadelphia, October 16, 1958. Dr. George Morris Piersol, M.A.C.P., Emeritus Dean and Emeritus Professor of Medicine, Graduate School, University of Pennsylvania, served as toastmaster at a dinner preceding the business meeting. Dr. Elbert L. Persons, F.A.C.P., Durham, N. C., President of the American Society of Internal Medicine, and Dr. James D. Weaver, President-Elect of the Pennsylvania Academy of General Practice, spoke on the relationships between the Internist and the General Practitioner. Mr. Robert L. Richards, newly-appointed Executive Secretary of the American Society of Internal Medicine, was introduced. Officers of the Society elected for the coming year were: Drs. John B. Tredway, F.A.C.P., Erie, President; Sidney O. Krasnoff, (Associate), Philadelphia, President-Elect; Wendell T. Jay, Jr., (Associate), Reading, Treasurer, and E. Buist Wells, F.A.C.P., Erie, Secretary.

Surgeon General's Consultant Group on Medical Education

The Surgeon General of the Public Health Service, Dr. Leroy E. Burney, F.A.C.P., conducted the first meeting of the Surgeon General's Consultant Group on Medical Education held on December 8, Washington, D. C., to discuss the subject, "How Can the Nation Be Supplied with Adequate Numbers of Well-Qualified Physicians over the Next Decade?" The group discussed the problem in the following manner: 1. Appraised the existing data, plans, and proposals related to medical schools and the Nation's needs for physicians; 2. Identified areas of agreement and those requiring further study; 3. Recommended general actions which might be taken

to achieve reasonable and acceptable goals in medical manpower during the next ten to twenty years; 4. Recommended specific actions which institutions, foundations, industry, local and state and federal governments should take in meeting these goals; 5. Recommended the role the Public Health Service should play and the steps which it should take.

Increased population, greater use of physicians' services, and advances in medical science indicate a period of increased demands for medical services in the next decade and beyond. There is evidence that existing medical schools, even with some expansion, cannot meet the present and potential needs. Among the members of the Consultant Group were the following members of the College: Drs. Ward Darley, F.A.C.P., Evanston, Ill.; Edward L. Turner, F.A.C.P., Chicago, Ill.; Edwin L. Crosby, F.A.C.P., Chicago, Ill., and Clayton G. Loosli, F.A.C.P., Los Angeles, Calif.

The Chicago Medical School Celebrates its 10th Anniversary

The Chicago Medical School marked the ten years of its accreditation and approval as a medical college of high standing at a dinner meeting held in Chicago, November 25, 1958. Dr. John J. Sheinin, President, gave a progress report and described the future plans for the development of the institution which includes a new medical research institute costing four million dollars and one of the first of seven buildings to be erected on ten acres of land in the heart of the Chicago West Side Medical Center.

American Society of Internal Medicine

The following members of the College have been recently elected officers of the State Societies of the American Society of Internal Medicine: Dr. Albert Aranson, (Associate), Portland, President, Maine Society of Internal Medicine; Dr. John H. Hornbaker, F.A.C.P., Hagerstown, President, Maryland Society of Internal Medicine; Dr. Walter P. Martin, F.A.C.P., Long Beach, President, California Society of Internal Medicine; Dr. John B. Treaway, F.A.C.P., Harrisburg, President, Pennsylvania Society of Internal Medicine; Dr. E. Buist Wells, F.A.C.P., Erie, Secretary, Pennsylvania Society of Internal Medicine, and Dr. G. Marshall Whitacre, F.A.C.P., Tacoma, President, Washington State Society of Internal Medicine.

International Congress of Gastroenterology

The 6th Meeting of the Association of the National European and Mediterranean Societies of Gastroenterology, organized by the Association of Dutch Gastroenterologists, will be held in Leiden, Netherlands, from April 20–24, 1960.

The main themes of the conference will be: "Pathology of the Small Intestine" and "Hepatitis, Cirrhosis Hepatitis and Their Possible Connection." Original reports on these subjects or any other gastroenterological subject, either clinical or in the field of basic sciences, are invited for submission and will be accepted for panel discussion or publication if approved by the Scientific Program Committee.

The official language will be English, but working languages will also include French, German and Spanish, with simultaneous translation. Advance registration fee will be $45.00, including the official reception, the banquet and an excursion. After November 1, 1959, the fee will be $55.00. For information write to the Congress Office of the 6th Meeting of the Association of the National European and Mediterranean Societies of Gastroenterology, Department of Gastroenterology, University Hospital, Leiden, the Netherlands, or the Secretary of the national societies of gastroenterologists.

American Congress of Physical Medicine and Rehabilitation

The American Congress of Physical Medicine and Rehabilitation will hold its 37th Annual Scientific and Clinical Session in Minneapolis, Minn., August 30–September 4, 1959. For information, write Dorothy C. Augustin, Executive Secretary, American Congress of Physical Medicine and Rehabilitation, 30 N. Michigan Ave., Chicago 2, Ill.

American Society of Internal Medicine

The Third Annual Meeting of the American Society of Internal Medicine will be held at the Conrad Hilton Hotel, Chicago, Ill., on April 19, 1959, immediately preceding the annual meeting of the American College of Physicians. A program and advance registration card will be sent to all individual members of ASIM during this month. Prompt return of the advance registration card is requested of all who plan to attend. All members of ASIM are cordially invited to attend the meeting, though only seated delegates will have the right to vote. The Committees of ASIM will meet on April 17–18, 1959, at the same location. Members and guests are also welcome to attend these meetings. For further information write to Clyde C. Greene, Jr., M.D., Assistant Secretary-Treasurer, American Society of Internal Medicine, 350 Post St., San Francisco 8, Calif.

American College of Allergists Meeting

The American College of Allergists Graduate Instructional Course and Annual Congress will be held in San Francisco, Calif., March 15–20, 1959. For information, write John D. Gillaspie, M.D., Treasurer, 2049 Broadway, Boulder, Colo.

Editor of the Journal of the American Medical Association Resigns

Dr. F. J. L. Blasingame, Executive Vice President of the American Medical Association, announced the resignation of Dr. Austin Smith as Editor of *The Journal of the American Medical Association* on December 15, 1958. Dr. Smith served as Editor of *The Journal* since 1949 when he succeeded Dr. Morris Fishbein. He joined the American Medical Association in February, 1940, as a Medical Consultant, becoming Secretary of the Council on Drugs in 1942. In 1946, he was named Director of the Division of Therapy and Research.

Dr. J. F. Hammond, former Associate Editor of *The Journal* was named Editor succeeding Dr. Smith.

Symposium on Hypertension

The Hahnemann Medical College and Hospital of Philadelphia conducted a Symposium on Hypertension in Philadelphia, Pa., December 8–12, 1958. Subjects discussed included: "Pathology and Clinical Aspects of Hypertension"; "Basic Concepts of the Etiology of Hypertension"; "Pharmacology of Hypertension and the Use of Sympathetic Blocking Agents"; "The Role of Salt and Diuretics in the Therapy of Hypertension." Panel discussions were held on the following subjects: "Development of an Effective Therapeutic Program"; "The Effect of Therapy on Prognosis in Patients with Hypertension," and "The Surgical Approach to Essential Hyperten-

sion." Dr. John H. Moyer, III, (Associate), Professor of Medicine, Hahnemann Medical College and Hospital of Philadelphia, was Chairman, and many members of the College were participants on the program.

2nd World Conference on Medical Education

Medical educators from more than 62 countries will meet at the Palmer House, Chicago, Ill., August 30–September 4, 1959, to exchange information and consider the problems of graduate, postgraduate and continuing education for the doctors of the world. "Medicine—A Lifelong Study" will be the theme of the 2nd World Conference on Medical Education organized and sponsored by The World Medical Association in collaboration with the World Health Organization, the International Association of Universities, and the Council for International Organizations of Medical Sciences. The Program Committee has invited approximately 125 speakers from more than 55 countries to present papers and has planned the program with a view toward devoting adequate time for discussion on each topic. Simultaneous translation in English, French, and Spanish will facilitate the exchange of ideas among the world's leading medical educators, investigators and practitioners as they seek efficient application of medical methods for assisting every doctor to increase his knowledge of medicine concomitantly with the rapid advances in medical science.

In addition to the didactic program, the American Medical Association and Association of American Medical Colleges, as Conference hosts, are offering pre- and post-convention tours to various centers of medical education. During the Conference week, the five medical schools in the Chicago area will be open for observation and comparison by the Conference participants. These schools represent the three prevalent systems in the U. S. A. for providing medical education, namely: schools owned and operated by non-governmental, non-religious associations; religious ownership and operation; and governmental management. Scientific advances in technology and the psychology of education will be combined to demonstrate the effectiveness of their application in medical education.

For additional information write The World Medical Association, 10 Columbus Circle, New York 19, N. Y.

Information Desired on Professional Personnel in Field of Rheumatic Disease

Because of the number of new units for the study of rheumatic diseases that are being established in medical schools in this country and abroad, there has grown a need for information about available personnel to staff such units. There is also current need for information regarding fellowship and traineeship opportunities in rheumatic diseases in the United States and other countries, and regarding potential and available candidates. Information is needed concerning opportunities for temporary exchanges of personnel between medical schools here and abroad.

In the hope of assisting in collection and dissemination of information on these and related questions, the American Rheumatism Association has recently established a Committee for the Exchange of Information Concerning Faculty Appointees and Fellows (EICFAF). The Committee will be pleased to receive information about fellowship and traineeship opportunities and faculty and other staff vacancies, as well as inquiries regarding available personnel. Such information and inquiries should be addressed to: Dr. Currier McEwen, New York University College of Medicine, 550 First Avenue, New York 16, N. Y.

University of California Medical Center Opens New Cardiovascular Research Institute

The Cardiovascular Research Institute of the University of California Medical Center, San Francisco, Calif., is in full operation with a broad program of investigation of human circulation and its diseases. The Institute was dedicated October 30 in ceremonies at which Earl Warren, Chief Justice of the United States, was principal speaker. Dr. Julius H. Comroe, Jr., F.A.C.P., Professor of Physiology, is Director.

The Institute occupies the entire 13th floor of the Herbert C. Moffitt Hospital. Its 22 individual laboratories are equipped for studying the heart, lungs, blood vessels and kidneys at all levels (man, animals, tissues, cells) and by a variety of techniques (biochemical, biophysical, pharmacological, pathological, radiological, psychological). In addition, the Institute contains such special research and diagnostic facilities as an eight-bed clinical investigation area with its own metabolic diet kitchen; two radiologic areas for cardiovascular catheterization and biplane angiography; and preparation, injection and counting rooms for use of radioisotopes.

Faculty members on the Institute staff represent thirteen departments of the School of Medicine. Twenty-three pre- and post-doctoral research fellows and trainees are participating in investigative programs.

The Cardiovascular Research Institute's $1,000,000 physical plant was built with major support from the California Legislature and the United States Public Health Service. Other grants for equipment, research and training have been received from numerous public and private agencies.

Personal Notes

Dr. Paul Dudley White, M.A.C.P., Boston, Mass., was the featured speaker at a luncheon during the 6th Heart-in-Industry Conference sponsored by the Chicago Heart Association and the Chicago Association of Commerce and Industry on November 14, 1958, Chicago, Ill.

Dr. Woodford B. Troutman, F.A.C.P., Louisville, Ky., was re-elected Secretary of the Kentucky State Medical Association at its Annual Meeting at Louisville, Ky., September 23–25, 1958.

Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, Calif., President of the American College of Physicians, gave the 11th Annual Friedenwald Memorial Lecture on "The Diagnosis and Management of Functional Gastrointestinal Disorders" at the University of Maryland School of Medicine, Baltimore, on November 11, 1958.

Dr. Bernard J. Alpers, F.A.C.P., Philadelphia, Pa., delivered the 3rd Annual Aaron Brown Lecture, sponsored by the Phi Delta Epsilon Fraternity, Beta Xi Chapter at Georgetown University School of Medicine, Washington, D. C., on February 14, 1959. His subject was "Compensating Mechanisms in Cerebral Blood Flow."

Major General Otis O. Benson, Jr., F.A.C.P., U.S.A.F. (MC), Commandant of the School of Aviation Medicine, U. S. Air Force, Randolph Air Force Base, Tex., presided at a Symposium on Medical Problems of Space Flight at the Base on October 28, 1958.

The 43rd International Meeting of the Interstate Postgraduate Medical Association was held November 10–13, 1958, at Cleveland, Ohio, under the Presidency of Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala.

Dr. August R. Crane, F.A.C.P., Philadelphia, Pa., and Dr. Max M. Strumia, F.A.C.P., Bryn Mawr, Pa., were guest speakers at the 9th Biennial Meeting of the Southeastern States Cancer Seminar at Tampa, Fla., November 19–21, 1958. The seminar was presented by the Hillsborough County Medical Association and sponsored by the Florida Division of the American Cancer Society and the Florida State Board of Health, in cooperation with the Florida Medical Association.

Three Fellows of the College were elected officers of the New York Allergy Society at the November 17, 1958 meeting. They are Drs. S. Senior Sack, Flushing, N. Y., President-Elect; Joseph H. Fries, Brooklyn, N. Y., Treasurer, and Murray Dworetzky, New York, N. Y., Assistant Secretary-Treasurer.

Five Fellows and an Associate of the College were participants on the program of the Seminar on Medical Education for the Non-University Hospitals of New England, sponsored by the Department of Medical Education of the Beverly Hospital, Beverly, Mass., January 9–10, 1959. Drs. Alex M. Burgess, Sr., Providence, R. I., and John C. Leonard, Hartford, Conn., were Co-Chairmen; Dr. Jean A. Curran, Sr., F.A.C.P., Brooklyn, N. Y., discussed the subject, "The Community Teaching Hospital in Graduate Medical Education"; Dr. William J. Lahey, F.A.C.P., Hartford, Conn., "Aims and Objectives of the American Association of Directors of Medical Education," and Drs. James M. Faulkner, F.A.C.P., Boston, Mass., and Howard Levine (Associate), New Britain, Conn., were panelists on a symposium on "Considerations in the Maintenance of an Effective Teaching Program in the Non-University Hospital."

Seven members of the College participated in the 7th Annual Course in "Present Concepts in Internal Medicine" held at the Letterman Army Hospital, San Francisco, Calif., October 27–31, 1958. Colonel Fred H. Mowrey, F.A.C.P., Washington, D. C., was Director of the program and was assisted by Colonel Emmett L. Kehoe, F.A.C.P., Colonel Frederick J. Hughes, Jr. (Associate); Lieutenant Colonel Loren F. Parmley, F.A.C.P., and Major Forrest W. Pitts, F.A.C.P., all members of the Medical Corps of the United States Army from San Francisco. Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, President of the American College of Physicians, discussed "Functional Gastrointestinal Disease" and moderated a panel discussion on "Malabsorption Syndromes." Dr. William S. Middleton, M.A.C.P., Chief Medical Director, Veterans Administration, Washington, D. C., discussed the subject "Sarcoidosis" and participated in a panel discussion on "Illness Due to Treatment."

Dr. George E. Wakerlin, F.A.C.P., New York, N. Y., Medical Director of the American Heart Association, was guest speaker at the Los Angeles County Heart Association's Board of Directors' Meeting in Los Angeles, Calif., on December 11, 1958.

Dr. George C. Griffith, F.A.C.P., Professor of Medicine at the Southern California School of Medicine, in Los Angeles, Calif., presided at the special meeting of

the Board of Directors and Heart Fund Leaders of the Los Angeles County Heart Association on December 1, 1958.

Dr. Anthony C. Cipollaro, F.A.C.P., New York, N. Y., discussed the subject "Current Trends in Cutaneous Radiation Therapy," at the 17th Annual Meeting of the American Academy of Dermatology and Syphilology held in Chicago, Ill., December 6–7, 1958.

Dr. Jon V. Straumfjord, (Associate), Astoria, Ore., was appointed to the State Board of Medical Examiners by Governor Holmes of the State of Oregon.

Dr. James L. D. Roth, F.A.C.P., Merion, Pa., is Secretary-General of the newly-organized Bockus International Society of Gastroenterology which has been developed by the Alumni of the Graduate School of Medicine of the University of Pennsylvania. Dr. Henry L. Bockus, F.A.C.P., Chairman, Department of Internal Medicine, University of Pennsylvania Graduate School of Medicine, for whom the Society was named, was made Honorary President. The 1st Annual Meeting will be held in Philadelphia, Pa., June 3, 1959, at which time the group will study geographical differences in behavior patterns and epidemiology of diseases in different parts of the world.

Dr. William A. Sodeman, F.A.C.P., Dean and Professor of Medicine at the Jefferson Medical College and Hospital of Philadelphia, presented the annual Da Costa Oration at the meeting of the Philadelphia County Medical Society, in Philadelphia, Pa., on October 8, 1958.

Dr. Isadore W. Ginsburg, F.A.C.P., was promoted to Professor of Clinical Medicine and Dr. Norman Learner, F.A.C.P., to Clinical Professor of Medicine, at the Temple University School of Medicine, Philadelphia, Pa.

Dr. William B. Bean, F.A.C.P., Iowa City, Iowa, was Professor of Medicine and Head of the Department pro tem, at the Washington University School of Medicine, St. Louis, Mo., from November 2–8, 1958. While there, he stayed in the hospital, directed the service, joined in discussions of the C.P.C., and gave talks on "Useful Lesions in the Skin" and "Pain in the Chest."

Dr. Lemuel C. McGee, F.A.C.P., Medical Director, Hercules Powder Company, Wilmington, Del., is a member of the Medical Advisory Committee to the Social Security Administration of the U. S. Department of Health, Education and Welfare, which met on November 13, 1958, at Baltimore, Md., to discuss "A Sound and Workable Method of Determining Disability."

Dr. Russell A. Nelson, F.A.C.P., Director of the Johns Hopkins Hospital, Baltimore, Md., has been named President-Elect of the American Hospital Association.

Dr. Henry J. Bakst, F.A.C.P., Professor of Preventive Medicine, Boston University School of Medicine, Boston, Mass., received a grant of $30,186 from the

United States Department of Health, Education, and Welfare to finance a program for expanding rehabilitation training in medicine.

Dr. George A. Wolf, Jr., F.A.C.P., Burlington, Vt., returned recently from Iran, where he had been a Curriculum Consultant to the University of Teheran Medical School, under the sponsorship of the International Cooperation Administration.

Drs. Joseph J. Bunim, F.A.C.P., Bethesda, Md.; Gene H. Stollerman, F.A.C.P., Chicago, Ill.; Morris Ziff (Associate), New York, N. Y., and Philip S. Hench, F.A.C.P., Rochester, Minn., were participants at the 5th Interim Scientific Session of the American Rheumatism Association held at the Mayo Clinic, Rochester, Minn., December 6, 1958.

Dr. Glenn E. Horton, (Associate), Memphis, Tenn., was recently re-elected Secretary-Treasurer of the Memphis Thoracic Society for 1959.

Four Fellows of the College from Boston, Mass., participated in the program of the meeting of the New England Cardiovascular Society held in Boston, November 17, 1958. Included were: Drs. Robert W. Wilkins, Belton A. Burrows, Samuel Proger, and Louis Weinstein.

Drs. John W. Norcross, Donat P. Cyr, and Elmer W. Heffernon, all Fellows of the College from Boston, Mass., were speakers on a Symposium on Anemias sponsored by the Lahey Clinic Fellowship Lectures held in Boston, December 3 and December 10, 1958.

Dr. Julius Hiram Comroe, Jr., F.A.C.P., Director, Cardiovascular Research Institute and Professor of Physiology at the University of California School of Medicine, San Francisco, Calif., will discuss "Contributions of Pulmonary Physiology to Clinical Medicine," and Dr. Edwin Bennett Astwood, F.A.C.P., Staff Member of the New England Medical Center, Boston, Mass., "Management of Thyroid Disease," at several medical schools during February and March as speakers on the Squibb Centennial Lecture Program sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

Dr. Mayer A. Green, F.A.C.P., Pittsburgh, Pa., recently attended the 3rd International Congress of Allergy held in Paris, France. He presented a paper entitled "Atypical Pollenosis."

Dr. Henry A. Monat, F.A.C.P., Washington, D. C., presented a paper on "Cardiac Symptoms Masking Digestive Disorders" at the meeting of the American College of Gastroenterology, and one on "Sprue Diet in Ulcerative Colitis," at a meeting of the Southern Medical Association, both held recently in New Orleans, La.

Dr. Byrd S. Leavell, F.A.C.P., Charlottesville, Va., has been named Assistant Dean of the University of Virginia School of Medicine, succeeding Dr. Henry B. Mulholland, F.A.C.P., who has retired. Dr. Mulholland will continue his teaching duties as Professor of Internal Medicine.

Dr. Theodore Rothman, F.A.C.P., Beverly Hills, Calif., has been recently made a "Membre Titulaire" of the Société Francaise d'Histoire de la Médecine.

Dr. R. Bruce Logue, F.A.C.P., Atlanta, Ga., was presented with a Silver Distinguished Achievement Award by the Georgia Heart Association for the work he has done for that organization during the past ten years.

Dr. Christopher J. McLoughlin, F.A.C.P., Atlanta, Ga., was elected Chairman of the Board at a meeting of the Board of State Governors of the American Diabetes Association held in San Francisco, Calif., recently.

Dr. Arthur M. Knight, Jr., F.A.C.P., Waycross, Ga., was recently elected Vice President of the Georgia Heart Association at the 10th Annual Meeting of that Association held in Savannah, Ga.

Dr. Jack C. Norris, F.A.C.P., Atlanta, Ga., was honored by the Medical College of South Carolina, Charleston, S. C., for his "distinguished services in organized medicine, and for his many years of loyalty as an alumnus." Dr. Kenneth M. Lynch, F.A.C.P., President of the College, presented the citation at the National Alumni Banquet which was held in New Orleans, La., November 4, 1958. The award was the first to be given by the College.

Three Fellows of the College were elected as officers for 1958–59 at the 65th Annual Convention of the Association of Military Surgeons of the United States held November 19, 1958, at Washington, D. C. They are: Rear Admiral Richard A. Kern, (MC), U. S. Navy, Ret., Philadelphia, Pa., 1st Vice President; Dr. Leroy E. Burney, Surgeon General of U. S. Public Health Service, 2nd Vice President, and Rear Admiral Irwin L. Norman, (MC), U. S. Navy, 4th Vice President. The Founder's Medal was awarded to Dr. W. Edward Chamberlain, F.A.C.P., Arlington, Va., Special Assistant for Atomic Medicine, Veterans Administration, and to Dr. A. B. C. Knudson, F.A.C.P., Springfield, Va., Director of Physical Medicine and Rehabilitation Services, Veterans Administration. These awards are presented annually by the Association for outstanding contribution to military medicine and for meritorious service to the Association.

Dr. Phil B. Bleecker, Sr., F.A.C.P., Memphis, Tenn., has been named President of the Tennessee Society of Internal Medicine.

Dr. Benjamin B. Wells, F.A.C.P., Director of Professional Services at the Veterans Administration Hospital, New Orleans, La., has been recently appointed Director of Veterans Administration Medical Education Services with offices in Washington, D. C.

Dr. M. Jay Flipse, F.A.C.P., Miami, Fla., was recently elected First Vice President of the American College of Chest Physicians.

Dr. Robert J. Boucek, (Associate), North Miami Beach, Fla., recently received an award of 300 pounds sterling for his prize-winning paper on "The Effect of Tissue

Age and Sex Upon the Metabolism of Rat Collagen." The award was made by the Ciba Foundation as a part of an international competition for research related to aging.

Dr. Amoz I. Chernoff (Associate), Durham, N. C., has been appointed Professor of Research at the University of Tennessee Memorial Research Center and Hospital at Knoxville, Tenn.

Dr. William B. Thompson, (Associate), Oklahoma City, Okla., was recently elected President of the Oklahoma State Heart Association.

Dr. Aaron M. Lefkovits, F.A.C.P., was recently appointed an Assistant Professor of Medicine at the University of Tennessee College of Medicine, Memphis, Tenn.

Dr. Daniel E. Jenkins, F.A.C.P., Houston, Tex., was elected President of the Southern Chapter of the American College of Chest Physicians at the 15th Annual Meeting held in New Orleans, La., November 2–3, 1958.

Drs. Morton M. Ziskind, (Associate), and Howard A. Buechner, F.A.C.P., both of New Orleans, La., were elected President and Vice President respectively at a recent meeting of the Louisiana Chapter of the American College of Chest Physicians.

Dr. Samuel Weiss, F.A.C.P., New York, N. Y., was made an Honorary Citizen of New Orleans and received a plaque and a Key of the City from the Mayor at the Annual Convocation of the American College of Gastroenterology, October 1958. Following this he attended the Regional Meeting of the Mexican Chapter of the American College of Gastroenterology and participated in a discussion on "Abdominal Lymphadenopathy and Lower Right Quadrant Pain," at Mexico City.

Dr. Jerome Weiss, (Associate), New York, N. Y., presented a paper on "The Effects of Iproniazid and Similar Compounds on the Gastrointestinal Tract: A Clinical Evaluation," at the meeting of the New York Academy of Sciences, Section on Biology, November 21, 1958.

Dr. Andrew L. Banyai, F.A.C.P., Chicago, Ill., was a speaker at the scientific transactions of the International Colloquium on Resistant Infections arranged by the World Medical Association, United States Committee and Eaton Laboratories, and held at New York, N. Y., November 20–21, 1958.

Dr. William Kaufman, F.A.C.P., Bridgeport, Conn., was Chairman of the Psychosomatic Section of the Third International Congress of Allergology in Paris, France, and read a paper entitled, "Some Psychological Aspects of the Treatment of Food Allergies in Children."

Dr. Dale Groom, F.A.C.P., Charleston, S. C., presented a paper entitled "Coronary Disease in the Negroes of Haiti and the United States" at the Annual Meeting of the American Heart Association in San Francisco, Calif., October 24–27, 1958.

Dr. C. Warren Irvin, Jr., (Associate), Columbia, S. C., attended the 3rd World Congress of Cardiology in Brussels, Belgium in August, 1958.

Dr. Thomas B. Magath, F.A.C.P., Senior Consultant in Clinical Pathology, Mayo Clinic, and Professor of Clinical Pathology, Mayo Foundation, University of Minnesota, Rochester, Minn., was awarded the Ward Burdick Gold Medal "for the most meritorious contribution to Clinical Pathology" at the recent meeting of the American Society of Clinical Pathologists. He delivered the Ward Burdick lecture on "The Antigen of Echinococcus."

Dr. Richard E. D. Kepner, F.A.C.P., Honolulu, Hawaii, has been honored by election to the Corresponding Membership of the Indian Psychiatric Society, on the recommendation of Lt. Col. Kirpal Singh. Dr. Kepner addressed the Delhi Medical Association in 1953 and at that time met Col. Singh, who is the Chief Psychiatrist in the Indian Army, Vice President of the Indian Psychiatric Society, and a Corresponding Fellow of the American Psychiatric Association.

Dr. J. Burns Amberson, F.A.C.P., Professor of Medicine Emeritus, Columbia University College of Physicians and Surgeons, New York, N. Y., has been named General Director of the New York Tuberculosis and Health Association.

Five Fellows and an Associate of the College were members of panels at the Midwest Forum on Allergy sponsored by the Michigan Allergy Society and the Societies of Buffalo, Chicago, Cleveland, Ohio Valley, Pittsburgh and West Virginia, and held at Detroit, Mich., December 6–7, 1958. The four Fellows included: Drs. Karl D. Figley, Toledo, Ohio; Iredell M. Hinnant, Shaker Heights, Ohio; Howard Osgood, Buffalo, N. Y.; Frank Perlman, Portland, Ore., and Theodore L. Squier, Milwaukee, Wis. The Associate was Dr. Edward A. Carr, Jr., Ann Arbor, Mich.

Dr. William D. Robinson, F.A.C.P., has been named Chairman of the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich., succeeding Dr. Cyrus C. Sturgis, M.A.C.P., who resigned in February, 1957, to devote full time to the practice of medicine. During the intervening time, Dr. Paul S. Barker, F.A.C.P., served as Acting Chairman.

Dr. Thomas M. Durant, F.A.C.P., Head of the Department of Medicine, Temple University School of Medicine, Philadelphia, Pa., delivered the Annual Judd-Plummer Memorial Lecture on October 3, 1958 at the 34th Annual Meeting of the Alumni Association of the Mayo Foundation, Rochester, Minn. His subject was "Medical Education: Responsibilities and Potentialities."

Dr. Hastings H. Walker, F.A.C.P., Honolulu, T. H., A.C.P. Governor for Hawaii, and Superintendent of the Leahi Hospital, recently participated in the Conference on Tuberculosis held at American Samoa, sponsored by the South Pacific Commission.

Captain George L. Calvy, F.A.C.P., (MC) U. S. Navy, Chief of the Medical Service at the U. S. Naval Hospital, St. Albans, Long Island, N. Y., received the Edward Rhodes Stitt Award for 1958. The award, sponsored by the Pfizer Laboratories and made annually by the Association of Military Surgeons, was presented to Captain Calvy on November 19 at the 65th Annual Convention of the Association held in Washington, D. C. The award included a life membership in the Military Surgeons Organization, an engraved bronze plaque, and a $500 honorarium, and was presented "for the most outstanding contribution by a member of the Association in the field of antibiotic medicine."

Major General Dan C. Ogle, F.A.C.P., U. S. Air Force (MC), received a Distinguished Service Medal at ceremonies held in the Pentagon Building, Washington, D. C., November 18, 1958. The citation said in part, "General Ogle distinguished himself by exceptionally meritorious service to the United States in a position of great responsibility as Surgeon General, United States Air Force, from July 1954 to December 1958. His professional competence, in which a clear perception of the objectives to be attained have enabled the Medical Service to fully support the Air Force Mission in the jet-missile-space era."

Dr. Joseph G. Benton, F.A.C.P., New York, N. Y., was recently appointed Chairman of the new Department of Rehabilitation Medicine at the State University of New York College of Medicine at New York City and Director of the Rehabilitation Department in Kings County Hospital Center, Brooklyn, N. Y.

Dr. Milford O. Rouse, F.A.C.P., Dallas, Tex., President-Elect of the Southern Medical Association, presided at the dedication of the new $250,000 headquarters of that Association in Birmingham, Ala., on September 7, 1958. Dr. Arthur C. McCarty, Sr., F.A.C.P., Louisville, Ky., made an official presentation of a portrait of C. P. Loranz who served as Professional Relations Director of the organization for 46 years and led the building fund drive.

Dr. W. Donald Close, F.A.C.P., has been made head of a new medical division at the Indiana University School of Medicine at Indianapolis. He will be in charge of an expanded medical education program for physicians serving residencies and internships on the staffs of the University Hospitals and will be Medical Director.

Dr. George W. Thorn, F.A.C.P., Hersey Professor of Theory and Practice of Physic at the Harvard Medical School and Physician-in-Chief, Peter Bent Brigham Hospital, Boston, Mass., gave the second Maurice C. Pincoffs Lecture in Internal Medicine at the University of Maryland School of Medicine, Baltimore, Md., on December 15, 1958. His subject was "Adrenal Hyperfunction—Clinical Studies."

Dr. William B. Bean, F.A.C.P., Iowa City, Iowa, has been named a Regent to the National Library of Medicine by President Dwight D. Eisenhower. He will serve for a period of four years.

Rear Admiral Bartholomew W. Hogan, F.A.C.P., (MC) U. S. Navy and Surgeon General and Chief of the Bureau of Medicine and Surgery, participated in round table discussions at the Second National Congress on Rehabilitation of the Disabled which was held in Mexico City, Mexico, on November 17–22, 1958.

Dr. C. Wilmer Wirts, F.A.C.P., Associate Professor of Medicine, the Jefferson Medical College of Philadelphia, acted as Gastroenterologist Pro Tem at the Lovelace Clinic, Albuquerque, N. M., November 15–20, 1958.

Dr. Perk Lee Davis, F.A.C.P., Paoli, Pa., participated in a symposium on "Chemotherapy of Cancer" on November 12, 1958, at the M. D. Anderson Cancer Hospital, Houston, Tex.

Rear Admiral Edward C. Kenney, F.A.C.P., (MC), U. S. Navy, Assistant Chief of the Bureau of Medicine and Surgery for Personnel and Professional Operations, Washington, D. C., was a panel member at a discussion on "Conference on Federal Medical Service" in the Mid-Year Clinical Session of the American Medical Association held in Minneapolis, Minn., December 2–5, 1958.

OBITUARIES

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. James Harvey Black, F.A.C.P., Dallas, Tex., December 1, 1958.
Dr. Robert Chobot, F.A.C.P., New York, N. Y., September 26, 1958.
Dr. Beaumont Sandfield Cornell, F.A.C.P., Huntington, Ind., September 16, 1958.
Dr. George William Cumbler, F.A.C.P., New York, N. Y., November 14, 1958.
Dr. John Sebastian Derr, F.A.C.P., Frederick, Md., October 23, 1958.
Dr. Francis J. Geraghty, F.A.C.P., Baltimore, Md., November 1, 1958.
Dr. Joseph LeRoy Gilbert, F.A.C.P., Washington, D. C., November 13, 1958.
Dr. Alfred Mirron Glazer, (Associate), Cincinnati, Ohio, September 26, 1958.
Dr. Raymond Essex Lease, F.A.C.P., Oyster Bay, N. Y., September 3, 1958.
Dr. Samuel Aaron Loewenberg, F.A.C.P., Philadelphia, Pa., December 4, 1958.
Dr. Arthur B. Petersen, (Associate), Spokane, Wash., September 26, 1958.
Dr. George Hancock Wilson, F.A.C.P., Lexington, Ky., September 26, 1958.

DR. JOHN HOWARD HOLBROOK

Dr. John Howard Holbrook, F.A.C.P., died at this home at Ancaster, Ontario, on March 14, 1958, at the age of 82 years, from a coronary thrombosis. Dr. Holbrook was born on a farm in Southern Ontario, on October 2, 1876. After attending the local high school, he was a school teacher for several years, but as soon as he could manage it, he enrolled at the Faculty of Medicine, University of Toronto, graduating M.B., M.D., in 1906.

He then interned in the Hamilton General Hospital. The following year, in 1908, he accepted the Superintendency of the little 26 bed hospital, which a group of Hamilton citizens had started to fight the scourge of tuberculosis. This institution became the famous Mountain Sanatorium of Hamilton, and Dr. Holbrook remained Superintendent for 37 years, until his retirement in 1946. Under his aegis, the Sanatorium grew from a few tents on the brow of the escarpment overlooking Hamilton, into a great institution comprising many modern pavilions, its own farm, and the best that was to be had in staff and equipment. Dr. Holbrook's vision, his talent for organizing and administering, and above all, his tremendous capacity for imparting his enthusiasm to all with whom he worked, were responsible for the Mountain Sanatorium developing into the largest institution in the British Commonwealth for the treatment of tuberculosis.

Dr. Holbrook received many honors during his professional career. He was a member of the Canadian Medical Association, and the American Sanatorium Association. He was President of the Ontario Medical Association in 1932–33, President of the Hamilton Academy of Medicine in 1931, and of the Ontario Hospital Association in 1936–37. He belonged to the Canadian Tuberculosis Association, and the Toronto Academy of Medicine. He was President of the Hamilton Association for the Study of Science, Literature and Art, from 1929 to 1931. He was a Charter Fellow of the Royal Canadian College of Physicians. He became a Fellow of the American College of Physicians in 1934 and was Governor of the College for Ontario from 1938 to 1941.

In his death, Canadian medicine has lost a great leader in the fight against tuberculosis and an esteemed member of its Councils. He is survived by his widow, who resides at Westtown, Ancaster, Ontario.

W. Ford Connell, M.D., F.A.C.P.,
Governor for Ontario

DR. ALFRED LABENSKY

Dr. Alfred Labensky of New London, Connecticut, was born July 17, 1891, in New London and died in his home town on July 7, 1958, of metastatic carcinoma of the sigmoid colon.

Dr. Labensky received his M.D. from Yale University School of Medicine in 1921 and interned at the Alameda County Hospital in California from 1921 to 1922. During the successive sixteen years Dr. Labensky took postgraduate training in general medicine at the Connecticut Clinical Congress, The Johns Hopkins University School of Medicine and the University of Maryland School of Medicine. He also furthered his postgraduate training at the Postgraduate Institute of the Philadelphia County Medical Society in 1938.

Dr. Labensky was a member of the Attending Staff of the Lawrence and Memorial Associated Hospitals in New London, Connecticut, from 1924 until his death. He had served as Chief Physician at this institution since 1939 and as Chief of Staff since 1953. He was also Consulting Physician to the Connecticut College for Women, the Norwich State Hospital and the Seaside Tuberculosis Sanatorium in Waterford, Connecticut.

Dr. Labensky was a member of the American Medical Association; the New London Medical Society; the New London County Medical Association, of which he was President in 1933; the Connecticut State Medical Society, where he also served as a member of the House of Delegates. He was a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1941.

Dr. Labensky's only survivor is his brother, Joseph Labensky, of Los Angeles, California.

Dr. Labensky was a physician of the old school and had served his hospital, the city, county and state in numerous medical capacities. He was greatly admired by his patients and his medical colleagues and he will be severely missed by all of his friends and patients.

JOHN C. LEONARD, M.D., F.A.C.P.,
Governor for Connecticut

DR. LOUIS O. S. WALLACE

Dr. Louis O. S. Wallace, F.A.C.P., died in Manchester, New Hampshire on May 20, 1958. He was suffocated when fire destroyed his home. He was born at Gilford, New Hampshire, on December 2, 1887. Dr. Wallace received his M.D. degree at the University of Maryland School of Medicine in 1912.

After interning at the Maine State Hospital at Bangor, Maine, and taking postgraduate training in internal medicine at the Royal University and Infirmary, Edinburgh, Scotland, 1913–14, he practiced in Kalamazoo, Michigan, 1921–28, and in Eldridge, California, 1928–29. He was a Contract Surgeon, First District Civilian Conservation Corps at Fort Williams, Maine, from 1935–36. He practiced medicine for many years in Manchester, New Hampshire. During the First World War he was a First Lieutenant in the Medical Corps of the United States Army from 1918–20.

Dr. Wallace was a member of the American Medical Association; the American Psychiatric Association; the American Association for the Advancement of Science; the American Psychopathological Association; the New Hampshire Medical Society; the New England Psychiatric Association; the Merrimack County Medical Society and the Manchester Medical Society. He became a Fellow of the American College of Physicians in 1928.

Dr. Wallace is survived by his widow, Mrs. Emma Frances Wallace, residing at 119 Hall Street, Manchester, New Hampshire.

TENTATIVE PROGRAM

THE AMERICAN COLLEGE OF PHYSICIANS

Fortieth Annual Session

CHICAGO, ILLINOIS

April 20–24, 1959

CLINICAL SESSIONS, LECTURES, BASIC SCIENCES, CLINICAL INVESTIGATION AND CONVOCATION

Dwight L. Wilbur, San Francisco, Calif., President

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Eliot E. Foltz, Winnetka, Ill.

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Walter L. Palmer
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Howard Wakefield

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Frank E. Trobaugh, Jr.
Maurice H. Wald

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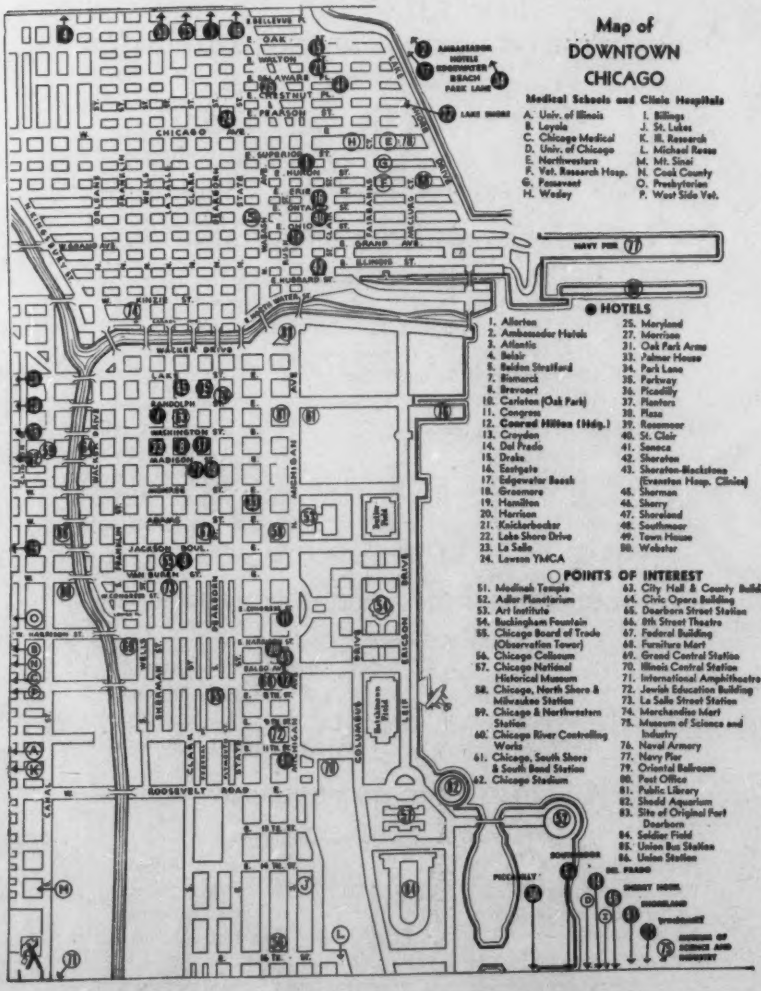


GENERAL INFORMATION

GENERAL HEADQUARTERS

CONRAD HILTON HOTEL

Registration headquarters, the information bureau, technical exhibits, scientific exhibits, clinical sessions, morning lectures, basic science and clinical investigation programs, panel discussions, clinical-basic science case conferences, color televised clinics, meetings of Committees, Board of Regents and Board of Governors. The Blackstone Theater, just across the street from the Conrad Hilton Hotel, and the 8th Street Theater, directly connecting with the Conrad Hilton Hotel, will be used for certain program features for which the Hotel does not have adequate accommodations. The Annual Convocation, the President's Reception and the Annual Banquet will all be held at the Hotel.

HOTEL ACCOMMODATIONS

The Conrad Hilton Hotel will be official headquarters for Officers, Regents, Governors, Committeemen and program participants. The following is only a limited list of hotels provided by the Chicago Convention Bureau, Suite 900, 134 N. La Salle St., Chicago 2, Ill. This Bureau will operate the Housing Bureau for this meeting. Official reservation form accompanies the final program. Additional copies may be obtained from the College Headquarters, 4200 Pine St., Philadelphia 4, Pa.

LIST OF HOTELS

Hotel	Total Rooms	For One Person	For Two Persons		Parlor Suites	
			Double Bed	Twin Beds	1 Bedroom	2 Bedrooms
*Conrad Hilton Hotel 720 S. Michigan Ave.	2000	$7.00–$17.50	$12.00–$21.00	$13.00–$27.00	$25.00 and up	$68.00 and up
Palmer House Hotel State & Monroe Sts.	400	8.00– 18.00	15.00– 22.50	16.00– 24.50	40.00 and up	65.00 and up
Congress Hotel 520 S. Michigan Ave.	350	7.00– 15.50	12.00– 19.00	12.00– 20.50	29.50 and up	33.00 and up
Hamilton Hotel 20 S. Dearborn St.	150	5.00– 8.00	8.00– 12.00	9.00– 13.00	18.00–50.00	
Sheraton-Blackstone Hotel 636 S. Michigan Ave.	155	8.50	15.00– 20.00	16.00– 22.00	26.00 and up	60.00 and up
Knickerbocker Hotel 163 E. Walton Place	150	8.80– 13.00	11.00– 15.00	11.00– 18.00	24.00 and up	40.00 and up
Shoreland Hotel 5454 S. Shore Drive	100	8.00– 15.00	10.00– 20.00	10.00– 20.00	20.00 and up	
Ambassador Hotel State & Goethe Sts.	50	15.50– 22.00	19.50– 28.00	19.50– 28.00	32.50 and up	
Eastgate Hotel 162 E. Ontario St.	75	7.00– 10.00	10.00– 14.00	11.00– 15.00	22.50–30.00	
St. Clair Hotel 162 E. Ohio St.	100	6.50– 12.00	9.00– 16.00	10.00– 18.00	22.50 and up	

* Headquarters.

Who May Register—

(*a*) All members of the American College of Physicians in good standing for 1959.

(*b*) All newly elected members.

(*c*) Members of the staff, including interns, residents and graduate medical students, of the Chicago participating Hospitals, without registration fee **upon presentation of proper identification;** admission to exhibits, clinical sessions, morning lectures, basic science programs, clinical investigation programs, clinical-basic science case conferences and TV programs (this does not include courtesy staff members).

(*d*) Graduate medical students pursuing courses in Chicago medical schools, without registration fee, **upon presentation of matriculation cards, or other evidence of registration at these institutions;** admission to exhibits, clinical sessions, morning lectures, basic science programs, clinical investigation programs, clinical-basic science case conferences and TV programs.

(*e*) Bona fide hospital residents, regardless of their location in North America, without registration fee, **upon presentation of proper credentials from their hospitals;** admission to exhibits, clinical sessions, morning lectures, basic science programs, clinical investigation programs, clinical-basic science case conferences and TV programs.

(*f*) Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force and Veterans Administration, either of the United States, Canada or Mexico, without registration fee, **upon presentation of proper credentials.**

(*g*) Qualified physicians, who may wish to attend this Session as visitors, sponsored in advance by letter or in person by a member of the College; such physicians shall pay a registration fee of $25.00, and shall be entitled to one specimen (current) copy of the ANNALS OF INTERNAL MEDICINE, unless they are already subscribers to the journal.

(*h*) Full-time medical teachers holding the rank of Assistant Professor or lower, **upon presentation of proper credentials from their medical schools,** shall be entitled to a reduction in the registration fee to $12.50.

The above regulations are essential because of the increasingly large attendance at the Annual Sessions of the College, and the necessity of accommodating members first.

Registration Bureau—While official registration will start on Monday morning, April 20, advance registration of members and exhibitors will be provided for by mail. The Registration Bureau will be set up for advance registration in the Conrad Hilton Hotel on Sunday, April 19, from 2:30 P.M. to 5:00 P.M. The Registration Bureau will be open throughout the week from 8:45 A.M. to 5:30 P.M.

Advance Registration of Members—In order to facilitate quick registration at the meeting for members of the College, an advance registration form, with directions, will be enclosed with the final Program to all Fellows and Associates. The success and justification of the plan is wholly dependent upon the cooperation of members, and thus the directions should be carefully noted and the proper forms returned to the Executive Offices of the College long in advance, so that each member's envelope of forms and badge will be ready for him when he calls at the Advance Registration Window. The use of this form will eliminate long lines and delays so frequently encountered at large conventions. A member, however, should not send in this form unless he is sure he is going to be present. Last year there was a 10% "no show" of advance registrations, resulting in waste of time and material.

Registration Blanks for Panel Discussions will be enclosed with the final program to members of the College. Non-members will secure registration blanks at the Registration Bureau during the Session.

Daily Bulletins—A Daily Bulletin of registrations will be published at this meeting.

Bulletin Board for special announcements will be located near the Registration Bureau.

Local Transportation—It is anticipated that the majority will utilize taxicabs, in which four can ride as cheaply as one. There is need for local transportation only in connection with the Hospital Clinics. Consult that portion of the Program for information about bus and other local forms of transportation.

Transportation for special features of Ladies Entertainment will be detailed in that portion of the Program.

Other Transportation Aids—At the Registration Bureau at the Conrad Hilton Hotel there will be a special transportation window where physicians can obtain information concerning train and plane schedules, and possibly make reservations.

The Annual Business Meeting of the College will be held at 1:45 P.M. on Thursday, April 23, immediately preceding the afternoon Clinical Session A-4 in the Grand Ballroom. All Masters and Fellows of the College are urged to be present. There will be the election of Officers, Regents and Governors and the annual reports of the Secretary-General, Executive Secretary and Treasurer. Announcements will be made of the Research Fellowship Awards, Latin-American Fellowship Awards, the A. Blaine Brower Traveling Scholarship Awards, the Elizabeth Archbold Bowes Traveling Scholarship Award, the Willard O. Thompson Memorial Traveling Scholarship Awards, and the Mead Johnson Residency Scholarship Awards. A revision of the Constitution and By-Laws will be presented for action. The President-Elect, Dr. Howard P. Lewis, Portland, Ore., will be inducted into office. Be present and know your College!

Board and Committee Meetings—All Board and Committee Meetings will be held at the Conrad Hilton Hotel according to a schedule which will appear in the Final Program. Special meetings will be announced and posted.

A Reception and Dinner, for members of the Board of Regents, Board of Governors, Committee Chairmen, distinguished guests and their wives, will be held Sunday, April 19, at 7:00 P.M., in the Waldorf Room, Conrad Hilton Hotel.

SPECIAL FEATURES

Invitation Session, Monday, April 20, 1959, 10:00 A.M., Waldorf Room, Conrad Hilton Hotel—A brand new feature in the Annual Sessions of the College will be a public meeting to which the officers of leading civic and lay societies will be invited. The purpose of this meeting is to acquaint the laity with the role of an Internist and the place of the American College of Physicians in North American Medicine. This will be accomplished by presenting a Panel Discussion on "The Care and Preservation of the American Executive." The opening remarks will be made by Dr. Eliot E. Foltz, General Chairman of the 40th Annual Session. President Dwight L. Wilbur will extend the welcome and a short briefing, and then will introduce the Panelists. The Panelists and their subjects include: "Arthritis and Rheumatism in their Relation to Busy Men and Women of Leadership," by Philip S. Hench, F.A.C.P.; "What is an Internist?," by Henry L. Bockus, F.A.C.P.; "Mental Health as it Pertains to Men and

Women under Pressure," by William C. Menninger, F.A.C.P.; "The Training of an Internist," by Chester M. Jones, M.A.C.P.; "Ulcers and their Importance to Business Men and Women," by Sara M. Jordan, F.A.C.P.; "The Role of an Internist in Medicine in the Community," by Howard P. Lewis, F.A.C.P.; "Heart Disease and its Relation to Busy Men and Women," by Irvine H. Page, F.A.C.P.; "What is the American College of Physicians?," by Walter L. Palmer, F.A.C.P.

President Wilbur will then give a brief summary of the Panel and introduce distinguished foreign guests and 1959 Medalists of the College. A brief reception will follow in the Astoria Room, with luncheon thereafter in the Waldorf Room.

Concert, Chicago Symphony Orchestra, Monday Evening, April 20, 8:15 P.M., Orchestra Hall, 216 S. Michigan Ave., Chicago—Orchestra Hall, which is the permanent home of the Chicago Symphony Orchestra, is between Jackson Boulevard and Adams Street on Michigan Avenue, and is easily within walking distance of the Conrad Hilton and other Loop hotels. The Committee on Entertainment is gratified to announce this Concert by the great Chicago Symphony Orchestra, under the direction of Fritz Reiner, who is planning a most attractive program for the College members. The citizens of Chicago are devoted to its great Orchestra, and it is a special privilege to have this Orchestra entertain the members of the College at a private Concert. There will be no charge of admission; tickets will be supplied at the Registration Desk of the College on request, first come, first served. Orchestra Hall seats about 2,700. Seats will be reserved only for Officers, Regents, Governors, distinguished guests, and their wives.

A Symphony Concert makes an ideal prologue for a scientific meeting. It will be one of the social highlights of the 40th Annual Session of the College.

Reception and Cocktails, tendered by the Governors of the College to new Associates and Direct Fellows: Astoria and Waldorf Rooms, Conrad Hilton Hotel, Tuesday, April 21, 5:30 P.M. to 7:30 P.M.—The Governors of the College extend an invitation to all new Associates and Direct Fellows, and their wives, who were elected on April 26, 1958, at Atlantic City, and on November 15, 1958, at Philadelphia, to attend a Reception and Cocktail Party on Tuesday evening, April 21, from 5:30 to 7:30 P.M. The receiving line will be in the Astoria Room, from whence the new members will proceed to the Waldorf Room to join their state contingents and their Governor. This occasion will provide opportunities for new members and their wives to meet the Officers and Regents, as well as to mingle with one another. Special invitations will be sent out by the Governors. *It is urged that acceptances or declinations be returned promptly to enable adequate planning.*

The Annual Convocation, the President's Reception and Dance: Wednesday Evening, April 22—The Annual Convocation of the College will be held at 8:30 P.M. in the Grand Ballroom of the Conrad Hilton Hotel. The President's Reception and Dance will follow at approximately 10:30 P.M. at the Conrad Hilton Hotel—receiving line in the Grand Assembly Room; the dance in the Grand Ballroom.

All members of the College and their families, and the public who are interested, are cordially invited to witness the impressive academic procession and other ceremonies. Tickets will not be required. All physicians elected Fellows of the College since the 1958 Convocation, and all previously elected Fellows who have not been formally inducted, should be present.

The Gowning Room from which academic regalia will be issued, will be Room 8, Third Floor of the Conrad Hilton Hotel. Robe rental forms will be supplied by the Executive Offices of the College to new Fellows several weeks in advance. Mr. Norman, of Bentley & Simon, suppliers of academic regalia, will be in charge of the Gowning Room, and robes will be picked up from and returned to this room.

The Pre-Convocation Assembly will form in the Normandie Lounge at 7:45 P.M. and the Academic Procession will move promptly at 8:40 o'clock to the Grand Ballroom. Officers, Regents, Governors and distinguished guests, candidates for Masterships and Honorary Fellowship will assemble at 8:00 o'clock in a special section of the Normandie Lounge.

The Convocation Ceremony will include the induction of new Fellows, an address by the President, and the Convocation Oration (title and speaker to be announced in the final program). The John Phillips Memorial Medal for 1959, the James D. Bruce Memorial Medal for 1959 and the Alfred Stengel Medal for 1959 will be awarded. Masterships will be conferred on three distinguished Fellows of the College and an Honorary Fellowship will be conferred on a distinguished foreign guest. There will be present officers or representatives of the American College of Surgeons, the American Medical Association, the Royal College of Physicians and Surgeons of Canada and the Royal College of Physicians of London, et al.

Immediately following the Convocation, the President's Reception will be held in the Grand Assembly Room. Dancing will start in the Grand Ballroom about 10:30 P.M., continuing to 1:00 A.M. The music will be provided by a well known orchestra, the Lou Breese Band. Tables for individual parties will be available around the periphery of the Ballroom.

The Annual Banquet: Grand Ballroom, Conrad Hilton Hotel, Thursday Evening, April 23, 8:00 P.M.—At 7:00 P.M. in the Normandie Lounge there will be a "Gratis" Cocktail Party for those holding banquet tickets.

At 8:00 P.M., in the Grand Ballroom, the Annual Banquet, dedicated to entertainment, relaxation and alimentation, will feature an outstanding Celebrity Show and music by Bud Dinwiddie's famous Orchestra.

And finally—a superb menu, devoid of dietary restrictions, and gratifying both gourmand and gourmet, will prepare you for this superlative entertainment.

Post-Convention Tour to Mexico—On Saturday, April 25, at 9:50 A.M., a special plane, or planes, will leave Chicago, via the American Airlines, arriving in Mexico City at 5:55 P.M. An alternate flight by coach leaves Chicago at 11:25 A.M., arriving in Mexico City at 8:30 P.M. Families and friends of College members and guests attending the 40th Annual Session of the College are cordially invited. The program in Mexico City is under the title "Seminars in Medicine of Mexico." The scientific programs will be conducted on Monday, Tuesday and Wednesday mornings, April 27, 28 and 29, at the National Institute of Cardiology and/or at other institutions. The National Institute of Cardiology is a mecca to which physicians interested in cardiology come from all parts of the world. The scientific program will be published and sent to all who subscribe to the Seminars. President of the College, Dr. Dwight L. Wilbur, and Mrs. Wilbur, will head the College group.

Mexico offers startling changes of scenery; majestic mountains and snow-topped volcanoes; lush green valleys; exotic tropical areas; colorful customs and contrasts. The headquarters hotel in Mexico City will be the Hotel Geneve. Sight-seeing tours are arranged for Xochomilco, a city inspection, the Pyramids, University City, Pedregal, Cuernavaca, Hacienda Vista Hermosa and Taxco. On May 1 the party will leave Mexico by American Airlines DC 7, non-stop to Chicago, or at 1:10 A.M. on May 2, via American Airlines coach, the latter with stops at San Antonio and Dallas. Members of the party may arrange their transportation for flights directly to their home cities.

The inclusive prices range from $339.00 (coach) to $377.56 (first-class). For all details, programs and reservations, consult Mr. Leon V. Arnold, Tour Conductor, 33 Washington Square West, New York 11, N. Y.

ENTERTAINMENT OF VISITING LADIES

The Committee on Ladies' Entertainment extends a cordial invitation to the wives and families of the members of the American College of Physicians to attend the meeting in Chicago. We sincerely hope that the program which is planned will prove interesting and enjoyable.

Headquarters for registration, tickets and reservations will be in the Lower Tower Room of the Conrad Hilton Hotel.

Certain of the entertainment features are limited in accommodations; in others, an advance estimate of attendance is essential. For these reasons, early return of reservation cards and early registration upon arrival in Chicago is earnestly requested.

The Information Desk

Lists of restaurants, theaters, shops, beauty parlors and places of interest are available.

LADIES' PROGRAM

Sunday, April 19

2:00 P.M. to 5:00 P.M.—Registration.
Lower Tower Room, Conrad Hilton Hotel.

Monday, April 20

9:00 A.M. to 4:00 P.M.—Registration.
Lower Tower Room, Conrad Hilton Hotel.

9:00 A.M. to 1:00 P.M.—"Open House."
Lower Tower Room, Conrad Hilton Hotel. After you have registered, we hope you will join us for coffee and a visit. We especially want you to meet the wives of the Deans and the wives of the Chairmen of the Departments of Medicine of the five medical schools that are located in Chicago. These ladies have graciously consented to preside over the coffee table.

10:00 A.M. to 12:00 M.
Mrs. Dwight L. Wilbur, the wife of the President of the American College of Physicians, cordially invites the wives of all newly elected Fellows and Associates, as well as those wives who are attending a meeting of the College for the first time, to meet with her in the South Bay of the Lower Tower Room.

2:00 P.M.—A Visit to The Art Institute of Chicago.
Members of the Museum Staff of The Art Institute will lecture briefly in the galleries devoted to the work of the Old Masters, Impressionists and 20th Century Painters. The guests are requested to meet in the Lobby of the Museum, Michigan Avenue at Adams Street. Tea will be served after the lectures. Reservations are limited. Tickets, $2.00.

8:15 P.M.
The Chicago Symphony Orchestra, under the direction of Fritz Reiner, will give a concert for the members of the American College of Physicians and their families. The doctors should procure the tickets at the men's Registration Desk, located in the lower lobby, Exhibition Floor, Conrad Hilton Hotel.

Tuesday, April 21

9:00 A.M. to 4:00 P.M.—Registration. Coffee will be served.
Lower Tower Room, Conrad Hilton Hotel.

9:00 A.M.—North Shore Tour and Luncheon.
To better acquaint you with our City and environs, there will be a tour along Chicago's famed lake front to Evanston, the home of Northwestern University. In Wilmette you will visit the magnificent Baha'i House of Worship, the headquarters of an interesting world wide faith. From there you will be driven through the beautiful residential areas of Kenilworth and Winnetka to "Edgecliff," the handsome home of Mr. Nathan S. Cummings. Mr. Cummings and his daughter and her husband, Mr. and Mrs. Robert B. Mayer, have graciously consented to show us their notable collection of modern art by such artists as Dufy, Renoir, Pissaro and Rouault. It is a privilege for us to have this opportunity. Following this there will be a luncheon in the Hawthorne Room of Marshall Field and Company's newest shopping center, Old Orchard. Buses will return to Chicago in mid-afternoon. Tickets, $8.00 (including transportation and luncheon).

Wednesday, April 22

9:00 A.M. to 4:00 P.M.—Registration. Coffee will be served.
Lower Tower Room, Conrad Hilton Hotel.

12:30 P.M.—Luncheon and Fashion Show.
Crystal Ballroom, Sheraton-Blackstone Hotel (across the street from the Conrad Hilton Hotel). Chicago is justly proud of this hotel with its tradition of gracious hospitality. Once again Marshall Field and Company will present a glamorous fashion show as a special treat for the College wives. Tickets, $6.00.

8:40 P.M.
Convocation in the Grand Ballroom, Conrad Hilton Hotel, followed by the President's Reception and Dance.

Thursday, April 23

9:00 A.M. to 12:00 M.—Registration.
Lower Tower Room, Conrad Hilton Hotel.

9:30 A.M.—"Around the World in 90 Minutes."
The world's most magnificent outlay of multi-million dollar displays featuring the finest in the field of home furnishings can be seen on this tour through our internationally known wholesale buying center, the Merchandise Mart. The Committee feels fortunate in being able to offer this unique tour as you will see display rooms that have never before been open to tours. Because of this, it is necessary to make your reservations as early as possible; an adequate number of guides must be specially trained. Tour tickets, $1.00.
Buses will leave the Conrad Hilton Hotel for the Merchandise Mart at 9:30 A.M. Following the tour, buses will take you to any one of four destinations: to Marshall Field and Company, if you care to shop; to the Kungsholm or the Chicago Yacht Club, if you plan to attend either of these luncheons; or to the Conrad Hilton Hotel. Bus fare (round trip), $1.50.

12:00 M.—Luncheon at the Kungsholm.

Once again at this beautiful Scandinavian restaurant there will be a Smorgasbord luncheon. Following this you will be the guests of the Kungsholm at a performance in the Miniature Grand Opera Theater, a small scale reproduction of the Royal Opera House in Copenhagen. The Opera will be "Madame Butterfly." The performers are puppets operated below stage by trained music students and are dressed in authentic costumes. Tickets, $4.00.

12:00 M.—Luncheon at the Chicago Yacht Club.

Foot of Monroe Street. This building, one of our newest, overlooks the Yacht Basin and shows our guests one of the delightful aspects of life in Chicago. Tickets, $4.00.

For the convenience of those who do not wish to take the tour of the Merchandise Mart, but who plan to attend either of the luncheons, a special bus will leave the Conrad Hilton Hotel promptly at 11:30 A.M. for the Kungsholm and the Chicago Yacht Club. After the luncheons, buses will return you to the Conrad Hilton Hotel or take you to the downtown shopping area. Bus fare (round trip), $1.50.

7:00 P.M.

Gratis Cocktail Party (for those holding banquet tickets). Normandie Lounge, Conrad Hilton Hotel.

8:00 P.M.—Annual Banquet of the College.

Grand Ballroom, Conrad Hilton Hotel. An outstanding Celebrity Show and music by Bud Dinwiddie's famous Orchestra.

ACKNOWLEDGMENT

The Wyeth Fund for Postgraduate Medical Education has made a generous grant-in-aid to the American College of Physicians for the support of that portion of the program devoted to the Basic Sciences, particularly toward defraying travel expenses for outstanding young, full-time teachers and researchers, non-members of the College, who will be contributing to the program. The Wyeth Fund for some years has been making useful contributions to medical education; it supports fellowships for residency training, unrestricted grants to medical schools and to pharmacy schools.

SUPPLEMENTARY GROUP MEETINGS

American Society of Internal Medicine, Dr. Elbert L. Persons, President—meetings at Conrad Hilton Hotel. Committee meeting, Saturday, April 18, Rooms 12 and 13, 4th floor; General Session, Sunday, April 19, Waldorf Room.

Cleveland Clinic Foundation is planning an invitation reception and cocktail party for all former fellows of the Cleveland Clinic, and their wives (consult the Final Program and the Bulletin Board at the Annual Session for final details, date, hours and place).

Tri-Services Social Hour—The Armed Forces Medical Services (Army, Air Force and Navy Medical Departments) are sponsoring a Social Hour on Thursday evening, April 23, 1959, from 6:30 P.M. to 8:00 P.M., at the Conrad Hilton Hotel, Waldorf Room. The Commanding Officer of the U. S. Naval Hospital, Great Lakes, Ill., is in charge of local arrangements. All Associates and Fellows of the American College of Physicians who are in the Army, Air Force and Navy, their wives and their guests, are cordially invited. The Social Hour will immediately precede the

Annual Banquet of the College (consult the Final Program and the Bulletin Board at the Annual Session for further details).

Reunion, University of Illinois Research and Educational Hospital Medical Alumni—A dinner-meeting, Tuesday, April 21, 1959, at 6:30 P.M., Union Building of the University of Illinois, 739 S. Wood Street. Dr. Ronald E. Fox, 111 N. Wabash Avenue, Chicago 2, Ill., in charge.

Governors' Receptions and Cocktail Parties—Several Governors are planning receptions and cocktail parties for members from their particular states or territories some time during the week (consult Bulletin Board at the Annual Session for listings).

SCIENTIFIC EXHIBITS

Exhibition Floor, Conrad Hilton Hotel

The Board of Regents, acknowledging that certain topics can best be demonstrated by a Scientific Exhibit, rather than by a formal paper, has authorized a limited Scientific Exhibit at this Session, selected by the President. Exhibits of a few national societies are also included.

Space S.E.-1 Cancer of the Colon and Rectum.
American Cancer Society, Inc., New York, N. Y.

Space S.E.-2 Common Ocular Problems.
DAN M. GORDON, M.D., New York, N. Y.
The L. Margolyes League, New York Hospital, Cornell Medical Center.

Space S.E.-3 The National Clearing House Program.
American Association of Blood Banks, Miami, Fla.

Space S.E.-4 Circumscribed Pulmonary Lesions: A Plea against Complacency.
ROBERT W. JAMPLIS, M.D.
J. IAN McNEILL, M.D.
SIDNEY P. MITCHELL, F.A.C.P.
FRANCIS S. NORTH, M.D.
JOHN F. WEIGEN, M.D.
GEORGE A. WOOD, M.D.
Palo Alto Medical Clinic, Palo Alto, Calif.

Space S.E.-5 Current Management of Adult Pneumonia in Hospital Practice.
VERGIL N. SLEE, (Associate), Director, Ann Arbor, Mich.
Commission on Professional and Hospital Activities, Inc.

Space S.E.-6 A New Oral Hypoglycemic Agent—Phenformin(DBI).
CHARLES WELLER, JR., F.A.C.P.
A. MACAULAY, M.D.
Grasslands Hospital, Valhalla, N. Y.
LEO P. KRALL, (Associate)
ROBERT F. BRADLEY, JR., (Associate)
PRISCILLA WHITE, F.A.C.P.
Joslin Clinic, Boston, Mass.
J. POMERANZE, M.D.
R. GADEK, M.D.
New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.

Space S.E.-7 Intestinal Biopsy Capsule.

Armed Forces Institute of Pathology, Washington, D. C.
WILLIAM H. CROSBY, JR., (Associate)
Lt. Colonel, MC, U. S. Army.
C. E. BUTTERWORTH, JR., M.D.
Major, MC, U. S. Army.
ROBERT W. SMITH, M.D.
Major, MC, U. S. Army.
Walter Reed Army Institute of Research.
BENJAMIN H. SULLIVAN, JR., F.A.C.P.
Colonel, MC, U. S. Army.
Walter Reed Army Hospital.

Space S.E.-8 Progress in the Management of Essential Hypertension.
GARFIELD G. DUNCAN, F.A.C.P., Philadelphia, Pa.

Space S.E.-9 Joint Commission on Accreditation of Hospitals.
KENNETH B. BABCOCK, M.D., Chicago, Ill.
Director.

Space S.E.-10 American Society of Internal Medicine, San Francisco, Calif.

Space S.E.-11 Neural Mechanism of Emesis and Anti-emesis: Site of Action of Emetic and Anti-emetic Agents.
WILLIAM AMOLS, M.D.
S. C. WANG, M.D.
H. HOUSTON MERRITT, M.D.
Columbia University College of Physicians and Surgeons, New York, N. Y.

Space S.E.-12 Test for Systemic Lupus Erythematosis.
HARRY E. THOMPSON, F.A.C.P.
K. K. JONES, Ph.D.
Clinical Research Laboratories, Tucson, Ariz.

Space S.E.-13 A Primer on Radiation Hazards.
RICHARD E. PETERSON, (Associate).
Chief, Radioisotope Service.
JULIUS G. BARON, M.D.
Chief, Radiology Service.
BARTIS M. KENT, M.D.
Clinician, Radioisotope Service.
TITUS C. EVANS, Ph.D.
Consultant in Radiobiology.
Veterans Administration Hospital, Iowa City, Iowa.

Space S.E.-14 The Manifestations of Muscular Dystrophy.
Muscular Dystrophy Associations of America, Inc., New York, N. Y.

Space S.E.-15 Opacifying Gallstones.
EMANUEL SALZMAN, M.D.
R. P. SPURCK, M.D.
L. C. KIER, Ph.D.
D. H. WATKINS, M.D.
Denver General Hospital and the University of Colorado School of Medicine, Denver, Colo.

Space S.E.-16 Laboratory Diagnosis of Aseptic Meningitis.
GILBERT DALLDORF, M.D.
H. HENRY W. KUMM, M.D.
The National Foundation, New York, N. Y.

Space S.E.-17 Standards of Practice of Internal Medicine in American Hospitals.
G. KARL FENN, F.A.C.P., Director of Study, Chicago, Ill.
ARTHUR R. COLWELL, F.A.C.P., Chairman of Committee, Chicago, Ill.
American College of Physicians.

Spaces S.E.-18 & 19 Early and Comprehensive Treatment of Parkinson's Disease.
LEWIS J. DOSHAY, M.D.
Columbia-Presbyterian Medical Center, New York, N. Y.

THE TECHNICAL EXHIBIT

Exhibition Floor, Conrad Hilton Hotel. There will be 148 Technical Exhibit Booths, with well over one hundred separate exhibitors. Irrelevant exhibits are eliminated, and only firms which present a group of approved products or services of scientific interest and real worth, will exhibit.

The Technical Exhibit is an important addition to the postgraduate medical education program of the meeting. The College Exhibit is always dignified in appearance, attractive and artistic. Exhibitors have been requested to select representatives who are already known by the profession—courteous, reserved, cheerful people, not overpowering super salesmen. Those manning pharmaceutical displays should be able to substantiate claims by reference to accepted research work or published material. Exhibitors are discouraged from distributing samples, except upon request, but rather to distribute freely samples and literature by mail to interested physicians after the meeting.

Exhibits will be open from 8:45 A.M. to 5:30 P.M., daily, Monday through Thursday, and from 8:45 A.M. to 12:15 P.M. on Friday. Technical Exhibitors gauge the meeting by the amount of interest shown and the co-operation displayed by members of the College. Their financial contributions aid materially in meeting the cost of the Annual Session and they deserve the courteous and interested attention of all physicians in attendance.

Partial List of Technical Exhibitors

	Booth
Abbott Laboratories, North Chicago, Ill.	89, 90
Alkalol Co., The, Taunton, Mass.	22
American Ferment Co., Inc.; New York, N. Y.	125
Ames Company, Inc., Elkhart, Ind.	51
Association of American University Presses, New Haven, Conn.	40
Astra Pharmaceutical Products, Inc., Worcester, Mass.	127
Audio-Digest Foundation, Glendale, Calif.	129
Ayerst Laboratories, New York, N. Y.	53, 54
W. A. Baum Co., Inc., Copiague, L. I., N. Y.	103
Baxter Laboratories, Inc., Norton Grove, Ill.	35
Becton, Dickinson and Company, Rutherford, N. J.	119
Blakiston Division, McGraw-Hill Book Co., Inc., New York, N. Y.	110
Borcherdt Company, Chicago, Ill.	24

	Booth
Bowen & Company, Inc., Bethesda, Md.	25
Brewer & Company, Inc., Worcester, Mass.	61
Burdick Corporation, The, Milton, Wis.	76
Burroughs Wellcome & Co. (U.S.A.), Inc., Tuckahoe, N. Y.	52
Burton, Parsons & Company, Washington, D. C.	41
Cambridge Instrument Co., Inc., New York, N. Y.	69
Carnation Company, Los Angeles, Calif.	131
Chicago Dietetic Supply House, Inc., The, Chicago, Ill.	121
Ciba Pharmaceutical Products, Inc., Summit, N. J.	57
Warren E. Collins, Inc., Boston, Mass.	16
Davies, Rose & Company, Limited, Boston, Mass.	132
F. A. Davis Company, Philadelphia, Pa.	81
Desitin Chemical Company, Providence, R. I.	82
Devereux Schools, Devon, Pa.	43
DeVilbiss Company, The, Somerset, Pa.	116
Dome Chemicals Inc., New York, N. Y.	109
Eaton Laboratories, Norwich, N. Y.	9, 10
Fenwal Laboratories, Somerville, N. J.	104
C. B. Fleet Company, Inc., Lynchburg, Va.	88
Flint, Eaton & Company, Decatur, Ill.	108
E. Fougera & Company, Inc., Hicksville, L. I., N. Y.	102
Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Yonkers, N. Y.	55, 56
General Foods Corporation, White Plains, N. Y.	77, 78
Gerber Baby Foods, Fremont, Mich.	146
Glenwood Laboratories, Inc., Bergenfield, N. J.	123
Grune & Stratton, Inc., New York, N. Y.	38, 39
Paul B. Hoeber, Inc., New York, N. Y.	44
Hollister-Stier Laboratories, Philadelphia, Pa.	100
Instrumentation Associates, New York, N. Y.	3
I.P.M.A. Publishing Company, Minneapolis, Minn.	147
Irwin, Neisler & Company, Decatur, Ill.	14
Ives-Cameron Company, Philadelphia, Pa.	27
Jones Metabolism Equipment Company, Chicago, Ill.	65
Knoll Pharmaceutical Company, Orange, N. J.	42
LaMotte Chemical Products Company, Chestertown, Md.	80
Lea & Febiger, Philadelphia, Pa.	63
Lederle Laboratories, Division, American Cyanamid Company, Pearl River, N. Y.	68
Thomas Leeming & Co., Inc., New York, N. Y.	114
Eli Lilly and Company, Indianapolis, Ind.	85, 86, 87
J. B. Lippincott Company, Philadelphia, Pa.	95

	Booth
Little, Brown & Company, Boston, Mass.	120
Lloyd Brothers, Inc., Cincinnati, Ohio	115
Macmillan Company, The, New York, N. Y.	33, 34
Massachusetts Indemnity & Life Insurance Company, Boston, Mass.	118
Massengill Pharmaceuticals, Bristol, Tenn.	117
McNeil Laboratories, Inc., Philadelphia, Pa.	73
Mead Johnson & Company, Evansville, Ind.	48, 49
Medco Products Company, Tulsa, Okla.	67
Medical Bureau, The, Chicago, Ill.	134
Medical Film Guild, Ltd., New York, N. Y.	4
Medical Protective Company, The, Fort Wayne, Ind.	20
Merck & Co., Inc., Rahway, N. J.	138, 139
Merck, Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia, Pa.	70, 91, 150, 151, 152
Wm. S. Merrell Company, The, Cincinnati, Ohio	15
Miles Reproducer Co., Inc., New York, N. Y.	106
Modern Medicine Publications, Inc., Minneapolis, Minn.	141
C. V. Mosby Company, The, St. Louis, Mo.	99
National Drug Company, The, Philadelphia, Pa.	96
Nordson Pharmaceutical Laboratories, Inc., Irvington, N. J.	23
Organon Inc., Orange, N. J.	136
Ortho Pharmaceutical Corporation, Raritan, N. J.	98
Parke, Davis & Company, Detroit, Mich.	12, 13
Pet Milk Company, St. Louis, Mo.	2
Pfizer Laboratories, Brooklyn, N. Y.	32
Pharmacia Laboratories, Inc., Rochester, Minn.	64
Photostat Corporation, Rochester, N. Y.	19
Purdue Frederick Company, The, New York, N. Y.	140
Puritan Compressed Gas Corp., Kansas City, Mo.	26
Ralston Purina Company, St. Louis, Mo.	137
Riker Laboratories, Inc., Northridge, Calif.	74, 75
Ritter Company, Inc., Rochester, N. Y.	135
A. H. Robins Company, Inc., Richmond, Va.	60
Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.	62
William H. Rorer, Inc., Philadelphia, Pa.	47
Sanborn Company, Waltham, Mass.	45, 46
Sandoz Pharmaceuticals, Hanover, N. J.	66
W. B. Saunders Company, Philadelphia, Pa.	92, 113
Schenlabs Pharmaceuticals, Inc., New York, N. Y.	28, 29
Schering Corporation, Bloomfield, N. J.	11
Schieffelin & Co., New York, N. Y.	148
G. D. Searle & Co., Chicago, Ill.	8
Sherman Laboratories, Detroit, Mich.	18
Smith, Kline & French Laboratories, Philadelphia, Pa.	93, 94, 111, 112
E. R. Squibb & Sons, New York, N. Y.	130
Stuart Company, The, Pasadena, Calif.	17

OUTLINE OF THE CHICAGO SESSION

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
9:00 A.M. to 11:00 A.M.	REGISTRATION AND INSPECTION OF EXHIBITS	Hospital Clinics (13)	Morning Lectures	Hospital Clinics (12)	Morning Lectures
9:00 A.M. to 11:15 A.M.		T V Clinics	T V Clinics	T V Clinics	T V Clinics
Staggered Intermissions		Intermission	Intermission	Intermission	Intermission
11:30 A.M. to 12:45 P.M.		Panels (6)	Panels (6)	Panels (6)	Panels (5)
11:30 A.M. to 12:45 P.M.		C.P.C.'s	C.P.C.'s	C.P.C.'s	C.P.C.'s
P.M. PROGRAMS Staggered intermissions except Friday, for inspection of Exhibits.	2:00 to 2:40 Opening Ceremonies	2:00 to 5:00	2:00 to 5:00	1:45 to 2:45 Annual Business Meeting	2:00 to 3:45
	2:40 to 5:00 Clinical Session A-1	Clinical Session A-2	Clinical Session A-3	2:45 to 5:00 Clinical Session A-4	Clinical Session A-5
	Clinical Session B-1	Clinical Session B-2	Clinical Session B-3	Clinical Session B-4	
	Basic Science Session—1	Basic Science Session—2	Basic Science Session—3	Basic Science Session—4	Basic Science Session—5
	Clinical Investigation Session—1	Clinical Investigation Session—2	Clinical Investigation Session—3	Clinical Investigation Session—4	
5:00 P.M. to 5:30 P.M.	Exhibits	Exhibits	Exhibits	Exhibits	
EVENING	Symphony Concert	Reception to New Members	Convocation and President's Reception	Annual Banquet	

	Booth
Testagar & Co., Inc., Detroit, Mich.	122
Upjohn Company, The, Kalamazoo, Mich.	50
U. S. Vitamin Corporation, New York, N. Y.	5, 6, 7
Wallace Laboratories, New Brunswick, N. J.	58, 59
Wampole Laboratories, Stamford, Conn.	101
Warner-Chilcott Laboratories, Morris Plains, N. J.	71, 72
Westwood Pharmaceuticals, Buffalo, N. Y.	107
White Laboratories, Inc., Kenilworth, N. J.	133
Williams & Wilkins Co., The, Baltimore, Md.	97
Winthrop Laboratories, New York, N. Y.	83, 84
Woodward Medical Personnel Bureau, Chicago, Ill.	79
Wyeth Laboratories, Philadelphia, Pa.	142, 143, 144, 145
Year Book Publishers, Inc., The, Chicago, Ill.	37
Yorke Publishing Co., Inc., The, New York, N. Y.	105

CLINICAL SESSIONS PROGRAM

CLINICAL SESSION A-1

Grand Ballroom, Conrad Hilton Hotel

Monday Afternoon, April 20, 1959

Presiding Officer

ELIOT E. FOLTZ, F.A.C.P., Winnetka, Ill.

General Chairman

P.M.

2:00 Invocation.

The Reverend HARRISON RAY ANDERSON.
Minister of the Fourth Presbyterian Church of Chicago.

Addresses of Welcome:

The Honorable WILLIAM G. STRATTON.
Governor of the State of Illinois.

The Honorable RICHARD J. DALEY.
Mayor of the City of Chicago.

EDWIN F. HIRSCH, F.A.C.P.
President, Chicago Medical Society.

LOWELL D. SNORF, F.A.C.P.
Vice President, Institute of Medicine of Chicago.

ERNEST G. McEWEN, F.A.C.P.
President, Chicago Society of Internal Medicine.

LOWELL T. COGGESHALL, F.A.C.P.
Chairman of the Deans Committee, Chicago Medical Schools.

Response to Addresses of Welcome:

DWIGHT L. WILBUR, F.A.C.P., San Francisco, Calif.
President, The American College of Physicians.

Presiding Officer

DWIGHT L. WILBUR, F.A.C.P., San Francisco, Calif.

President

2:30 Announcements.

2:35 Combined Diuretic and Steroid Therapy in Cirrhosis with Ascites.

ROBERT S. MORRISON, M.D., (by invitation), Boston, Mass.
Clinical Instructor in Medicine, Tufts University School of Medicine; Senior Physician, Lemuel Shattuck Hospital; Assistant in Medicine, Harvard Medical School.

THOMAS C. CHALMERS, (Associate), Boston, Mass.
Clinical Associate in Medicine, Harvard Medical School; Lecturer in Medicine, Tufts University School of Medicine; Chief of Medical Services, Lemuel Shattuck Hospital.

2:50 Renal Failure in Laennec's Cirrhosis of the Liver.

SOLOMON PAPPER, (Associate), Boston, Mass.
Associate Clinical Professor of Medicine, Tufts University School of Medicine; Assistant Chief of Medicine, Boston Veterans Administration Hospital.

JOSEPH L. BELSKY, M.D., (by invitation), Boston, Mass.
Teaching Fellow in Medicine, Tufts University School of Medicine; Resident in Medicine, Boston Veterans Administration Hospital.

KENNETH H. BLEIFER, M.D., (by invitation), Boston, Mass.
Teaching Fellow in Medicine, Tufts University School of Medicine; Resident in Medicine, Boston Veterans Administration Hospital.

3:10 Drug-Induced Hepatic Injuries.

HANS POPPER, F.A.C.P., New York, N. Y.
Professor of Pathology, Columbia University College of Physicians and Surgeons; Director, Department of Pathology, Mount Sinai Hospital.

FENTON SCHAFFNER, F.A.C.P., New York, N. Y.
Research Associate in Gastroenterology, Mount Sinai Hospital.

3:25 The Significance of Alterations in Serum Enzymes in the Diagnosis of Icteric and Non-Icteric Hepatic Disease.

FELIX WROBLEWSKI, F.A.C.P., New York, N. Y.
Assistant Professor of Clinical Medicine, Cornell University Medical College; Assistant Attending Physician, Memorial Medical Center for Cancer and Allied Diseases.

3:40 Percutaneous Splenic Pulp Manometry as an Aid in Diagnosis of Acute Upper Gastrointestinal Bleeding.

WILLIAM F. PANKE, M.D., (by invitation), New York, N. Y.
Clinical Assistant Surgeon and Fellow in Surgery, St. Vincent's Hospital.

AUGUSTO H. MORENO, M.D., (by invitation), New York, N. Y.
Research Associate in Surgery, St. Vincent's Hospital.

LOUIS M. ROUSSELOT, F.A.C.S., (by invitation), New York, N. Y.
Director of Surgery, St. Vincent's Hospital.

WILLIAM J. GRACE, F.A.C.P., New York, N. Y.
Director of Medicine, St. Vincent's Hospital.

3:55 **Atrophy of the Gastric Mucosa in Dogs Induced by a Preparation of Normal Human Gastric Juice.**

W. O. SMITH, M.D., (by invitation), Oklahoma City, Okla.
WALTER JOEL, M.D., (by invitation), Oklahoma City, Okla.
M. K. DuVAL, M.D., (by invitation), Oklahoma City, Okla.
W. L. HONSKA, M.D., (by invitation), Oklahoma City, Okla.
STEWART G. WOLF, JR., F.A.C.P., Oklahoma City, Okla.
Professor of Medicine, University of Oklahoma School of Medicine.

4:10 **Patterns of Tests of Intestinal Absorption Following Gastrectomy.**

ARTHUR B. FRENCH, (Associate), Ann Arbor, Mich.
Assistant Professor of Internal Medicine, University of Michigan Medical School.
MAKOTO ISHIKAWA, M.D., (by invitation), Ann Arbor, Mich.
Research Fellow in Internal Medicine, University of Michigan Medical School.
H. MARVIN POLLARD, F.A.C.P., Ann Arbor, Mich.
Professor of Internal Medicine, University of Michigan Medical School.

4:25 **A Critical Analysis of the Use of Azulfidine in Chronic Ulcerative Colitis.**

CHARLES G. MOERTEL, M.D., (by invitation), Rochester, Minn.
Section of Medicine, Mayo Clinic and Mayo Foundation.
J. ARNOLD BARGEN, F.A.C.P., Rochester, Minn.
Section of Medicine, Mayo Clinic and Mayo Foundation.

4:40 **Further Observations on the Mechanism of Ulcer Pain.**

E. CLINTON TEXTER, JR., (Associate), Chicago, Ill.
Assistant Professor of Medicine, Northwestern University Medical School.
GASTON R. VANTRAPPEN, M.D., (by invitation), Louvain, Belgium.
Instructor in Medicine, Universiteitsklinieken, St. Rafael.
HAROLD P. LAZAR, M.D., (by invitation), Chicago, Ill.
Trainee in Gastroenterology, Veterans Administration Research Hospital, Northwestern University Medical Center.
ERNESTO J. PULETTI, M.D., (by invitation), Chicago, Ill.
Trainee in Gastroenterology, Veterans Administration Research Hospital, Northwestern University Medical Center.
CLIFFORD J. BARBORKA, F.A.C.P., Chicago, Ill.
Associate Professor of Medicine, Northwestern University Medical School.

5:00 **ADJOURNMENT.**

CLINICAL SESSION A-2

Grand Ballroom, Conrad Hilton Hotel

Tuesday Afternoon, April 21, 1959

Presiding Officer

CHARLES A. DOAN, F.A.C.P., Columbus, Ohio
First Vice President

P.M.

2:00 **The James D. Bruce Memorial Lecture on Preventive Medicine: Status of the Rickettsioses in the United States.**

JOSEPH E. SMADEL, M.D., (by invitation), Bethesda, Md.
Associate Director, National Institutes of Health.

2:20 **Current Status of Chemotherapy of Systemic Fungal Disease.**

JOHN P. UTZ, (Associate), Bethesda, Md.
Chief, Infectious Disease Service, National Institute of Allergy and Infectious Diseases.

ALBERT TREGER, M.D., (by invitation), Bethesda, Md.
Clinical Associate, Infectious Disease Service, National Institute of Allergy and Infectious Diseases.

CHESTER W. EMMONS, Ph.D., (by invitation), Bethesda, Md.
Chief, Mycology Section, National Institute of Allergy and Infectious Diseases.

2:35 **Recent Developments in the Laboratory Diagnosis of Syphilis.**

WARFIELD GARSON, M.D., (by invitation), Chapel Hill, N. C.
Research Professor and Head of the Department of Experimental Medicine, School of Public Health, University of North Carolina; Director, Venereal Disease Experimental Laboratory, Communicable Disease Center, U. S. Public Health Service.

2:50 **The Clinical Course of Leptospirosis: Observations Based on a Study of Sixteen Sporadic Cases.**

GEORGE A. EDWARDS, M.D., (by invitation), Dallas, Tex.
Clinical Assistant Professor of Medicine, University of Texas Southwestern Medical School; Chief, Medical Service, Veterans Administration Hospital, McKinney.

3:05 **Clinical Manifestations of Pulmonary Blastomycosis.**

ROBERT S. ABERNATHY, (Associate), Little Rock, Ark.
Assistant Professor of Medicine, University of Arkansas School of Medicine.

3:20 **INTERMISSION.**

Presiding Officer

CHARLES H. DRENCKHAHN, F.A.C.P., Urbana, Ill.

Third Vice President

3:45 **Air Pollution and Bronchitis.**

ALBERT ROBERTS, M.D., (by invitation), Washington, D. C.
Chief, Clinical Investigations, Air Pollution Medical Program, Division of Special Health Services, U. S. Public Health Service.

4:00 **Congenital Anomalies of the Lung: Practical Aspects of Diagnosis and Treatment for the Internist.**

JAMES A. WIER, F.A.C.P., Denver, Colo.
Colonel, (MC), U. S. Army; Chief, Pulmonary Disease Service, Fitzsimons Army Hospital.

4:15 The Reliability of Tissue Diagnosis in Pleurisy: A Preliminary Report.

JOEL H. RICHERT, (Associate), Denver, Colo.
Major, (MC), U. S. Army; Chief, Non-TB Chest Section, Fitzsimons Army Hospital.

JAMES A. WIER, F.A.C.P., Denver, Colo.
Colonel, (MC), U. S. Army; Chief, Pulmonary Disease Service, Fitzsimons Army Hospital.

JOHN M. SALYER, M.D., (by invitation), Denver, Colo.
Colonel, (MC), U. S. Army; Chief, Thoracic Surgery Service, Fitzsimons Army Hospital.

JAMES C. BEYER, M.D., (by invitation), Denver, Colo.
Major, (MC), U. S. Army; Department of Pathology, Fitzsimons Army Hospital.

4:30 The Results of the Experimental Use of Sulfur Dioxide in the Production of Material for Cell Studies in Lung Cancer.

WARDE B. ALLAN, F.A.C.P., Baltimore, Md.
Associate Professor of Medicine, Johns Hopkins University School of Medicine.

PHILIP WHITTLESEY, M.D., (by invitation), Baltimore, Md.
Instructor in Medicine, Johns Hopkins University School of Medicine.

4:45 Chemical and Morphological Studies on Pulmonary Elastic Tissue.

MARTIN J. FitzPATRICK, (Associate), Kansas City, Kans.
Associate Professor of Medicine, University of Kansas School of Medicine; Chief of Section for Pulmonary Disease and Director of Lerrigo Memorial Laboratory, University of Kansas Medical Center.

V. D. HOSPELHORN, Ph.D., (by invitation), Kansas City, Kans.
Assistant Professor of Medicine, University of Kansas School of Medicine; Lerrigo Memorial Laboratory, Department of Medicine, University of Kansas Medical Center.

5:00 ADJOURNMENT.

CLINICAL SESSION A-3

Grand Ballroom, Conrad Hilton Hotel

Wednesday Afternoon, April 22, 1959

Presiding Officer

WALLACE M. YATER, F.A.C.P., Washington, D. C.

Secretary General

P.M.

2:00 Studies in the Viral Etiology of Leukemia.

BILL P. MADUROS, M.D., (by invitation), Chicago, Ill.
Research Associate, The Hektoen Institute for Medical Research of the Cook County Hospital.

STEVEN O. SCHWARTZ, F.A.C.P., Chicago, Ill.
Director, Department of Hematology, The Hektoen Institute for Medical Research of the Cook County Hospital.

HAROLD M. SCHOOLMAN, (Associate), Chicago, Ill.
Research Associate, The Hektoen Institute for Medical Research of the Cook County Hospital.

2:15 **Meningeal Involvement in Acute Leukemia.**

RICHARD K. SHAW, M.D., (by invitation), Bethesda, Md.
Clinical Associate, National Cancer Institute.

EDWARD W. MOORE, M.D., (by invitation), Bethedsa, Md.
Clinical Associate, National Cancer Institute.

EMIL J. FREIREICH, M.D., (by invitation), Bethesda, Md.
Senior Investigator, National Cancer Institute.

2:30 **The Significance and Nomenclature of Blood Clotting Factors.**

IRVING S. WRIGHT, F.A.C.P., New York, N. Y.
Professor of Clinical Medicine, Cornell University Medical College.

2:45 **A Study of Systemic Lupus Erythematosus (S.L.E.) Occurring after Seventy-eight (78) Splenectomies for "Idiopathic" Thrombocytopenic Purpura (I.T.P.).**

YALE RABINOWITZ, M.D., (by invitation), Boston, Mass.
Research Fellow in Hematology, Tufts University School of Medicine and New England Center Hospital.

WILLIAM DAMESHEK, F.A.C.P., Boston, Mass.
Professor of Medicine, Tufts University School of Medicine; Hematologist-in-Chief and Director of Blood Research Laboratory, New England Center Hospital.

3:00 **The Dynamics of Leukopenia and Leukocytosis.**

C. G. CRADDOCK, JR., (Associate), Los Angeles, Calif.
Associate Professor of Medicine, University of California School of Medicine at Los Angeles.

SEYMOUR M. PERRY, (Associate), Los Angeles, Calif.
Assistant Professor of Medicine in Residence, University of California School of Medicine at Los Angeles.

JOHN S. LAWRENCE, F.A.C.P., Los Angeles, Calif.
Professor and Chairman of the Department of Medicine, University of California School of Medicine at Los Angeles.

3:15 **Some Observations on the Treatment of Post-Irradiation Hematopoietic Depression in Man by the Infusion of Stored Autogenous Bone Marrow.**

N. B. KURNICK, F.A.C.P., Los Angeles, Calif.
Associate Clinical Professor of Medicine, University of California School of Medicine at Los Angeles; Chief, Hematology Section, Veterans Administration Hospital, Long Beach.

BERNARD H. FEDER, M.D., (by invitation), Los Angeles, Calif.
Assistant Clinical Professor of Radiology, University of California School of Medicine at Los Angeles; Acting Chief, Radiology Service, Veterans Administration Hospital, Long Beach.

ANDREW MONTANO, (by invitation), Los Angeles, Calif.
Graduate Research Chemist, University of California School of Medicine at Los Angeles.

JAMES C. GERDES, M.D., (by invitation), Long Beach, Calif.
Staff Pathologist, Laboratory Service, Veterans Administration Hospital.

3:30 **INTERMISSION.**

Presiding Officer

FULLER B. BAILEY, F.A.C.P., Salt Lake City, Utah

Regent, A.C.P.

4:00 **Newer Physiology of Absorption from the Intestine.**

RICHARD J. REITEMEIER, M.D., (by invitation), Rochester, Minn.
Consultant in Medicine, Mayo Clinic; Instructor in Medicine, University of Minnesota (Mayo Foundation).

4:15 **Absorption of Radioactive B_{12} in Patients with Pernicious Anemia after Long Term Oral and Parenteral Therapy.**

PAUL J. FOUTS, F.A.C.P., Indianapolis, Ind.
Chief of Service, Department of Medicine, Lilly Laboratory for Clinical Research, Indianapolis General Hospital.

OSCAR M. HELMER, Ph.D., (by invitation), Indianapolis, Ind.
Head, Physiological Chemistry Department, Lilly Laboratory for Clinical Research, Indianapolis General Hospital.

STANLEY M. CHERNISH, M.D., (by invitation), Indianapolis, Ind.
Associate Visiting Physician, Lilly Laboratory for Clinical Research, Indianapolis General Hospital.

4:30 **A Study of the Role of Acute Infections in Precipitating Crises in Chronic Hemolytic States.**

CLAUDE-STARR WRIGHT, F.A.C.P., Augusta, Ga.
Professor of Medicine, Medical College of Georgia.

EDWARD GARDNER, JR., Ph.D., (by invitation), Augusta, Ga.
Assistant Research Professor of Medicine, Medical College of Georgia.

4:45 **The Oxyhemoglobin Dissociation Curve in Anemia.**

THEODORE RODMAN, M.D., (by invitation), Philadelphia, Pa.
Instructor in Medicine, Temple University School of Medicine; Staff Physician, Veterans Administration Hospital.

HENRY P. CLOSE, F.A.C.P., Philadelphia, Pa.
Professor of Clinical Medicine, Temple University School of Medicine; Chief of Medicine, Veterans Administration Hospital.

MAY K. PURCELL, (by invitation), Philadelphia, Pa.
Chief Technician, Cardiopulmonary Function Laboratory, Veterans Administration Hospital.

5:00 **ADJOURNMENT.**

ANNUAL CONVOCATION

Wednesday Evening, April 22, 1959

8:40 o'Clock

Grand Ballroom, Conrad Hilton Hotel

R. Carmichael Tilghman, Marshal

James W. Haviland, Assistant Marshal

John S. Graettinger, Assistant to the Marshal

Fellows to be inducted, Officers, Regents, Governors, Distinguished Guests, and Recipients of Awards; Gowning 7:00 P.M., Normandie Lounge, Conrad Hilton Hotel. Pre-Convocation Assembly, 7:45 P.M., Normandie Lounge, Conrad Hilton Hotel.

All Members of the profession and the general public are cordially invited.

1. Processional.
2. The President's Address.
   DWIGHT L. WILBUR.
3. Conferring of Fellowships by the President.
4. Conferring of Honorary Fellowship by the President.
5. Conferring of Masterships by the President.
6. Presentation of the James D. Bruce Memorial Medal for 1959.
7. Presentation of the John Phillips Memorial Medal for 1959.
8. Presentation of the Alfred Stengel Memorial Award for 1959.
9. The Convocation Oration (speaker and title to be announced in formal Program).
10. Recessional.

The President's Reception will follow in the Grand Assembly Room (adjacent to the Grand Ballroom) at 10:30 o'clock. Dancing thereafter in the Grand Ballroom. A cordial invitation is extended to all members and guests, with their families.

CLINICAL SESSION A–4

Grand Ballroom, Conrad Hilton Hotel

Thursday Afternoon, April 23, 1959

Presiding Officer

DWIGHT L. WILBUR, F.A.C.P., San Francisco, Calif.

President

P.M.

1:45 THE ANNUAL BUSINESS MEETING

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Announcements will be made of the Research Fellowship Awards, Latin-American Fellowship Awards, the A. Blaine Brower Traveling Scholarship Awards, the Elizabeth Archbold Bowes Traveling Scholarship Award, the Willard O. Thompson Memorial Traveling Scholarship Awards and the Mead Johnson Residency

Scholarship Awards. Reports will be received from the Secretary-General, Executive Secretary and Treasurer; revision of the Constitution and By-Laws will be presented; election of new Officers, Regents and Governors will take place; President-Elect Howard P. Lewis, of Portland, Ore., will be inducted as President and will make a brief inaugural address.

Presiding Officer

HOWARD P. LEWIS, F.A.C.P., Portland, Ore.

President

2:45 **The Liver in Porphyria Cutanea.**

JAN WALDENSTROM, M.D., (by invitation), Malmo, Sweden.
Professor of Clinical Medicine, University of Lund.

3:00 **A Comparison of Dietary Habits and Serum Labids in Trappist and Benedictine Monks.**

J. GORDON BARROW, F.A.C.P., Atlanta, Ga.
Director, Heart Disease Control Program, Georgia Department of Public Health.

CARROLL B. QUINLAN, M.D., (by invitation), Atlanta, Ga.
Associate Director, Heart Disease Control Program, Georgia Department of Public Health.

GERALD R. COOPER, M.D., (by invitation), Atlanta, Ga.
Chief, Hematology and Biochemistry Section, Communicable Disease Center.

VIRGINIA S. WHITNER, M.S., (by invitation), Atlanta, Ga.
Director, Research Lipid Laboratory, Georgia Department of Public Health.

MARY HELEN R. GOODLOE, B.S., (by invitation), Atlanta, Ga.
Research Nutritionist, Georgia Department of Public Health.

3:15 **Essential Familial Hypercholesterolemia: A Ten-Year Follow-up of a Large Kindred.**

CHARLES F. WILKINSON, JR., F.A.C.P., New York, N. Y.
Professor and Chairman of the Department of Medicine, New York University Post-Graduate Medical School.

WINNIFRED SEEGERS, M.D., (by invitation), New York, N. Y.
Assistant Professor, Department of Medicine, New York University Post-Graduate Medical School.

RICHARD C. BOZIAN, M.D., (by invitation), Nashville, Tenn.
Assistant Professor, Department of Biochemistry, Vanderbilt University School of Medicine (formerly at New York University Post-Graduate Medical School).

SETH WAKEMAN, Ph.D., (by invitation), Northampton, Mass.

J. MARION BRYANT, M.D., (by invitation), New York, N. Y.
Associate Professor, Department of Medicine, New York University Post-Graduate Medical School.

JOHN F. HEFFERNAN, M.D., (by invitation), New York, N. Y.
Instructor, Department of Medicine, New York University Post-Graduate Medical School.

IRA J. LAUFER, M.D., (by invitation), New York, N. Y.

3:30 **The Role of Heredity, Diet and Occupational Stress in Coronary Heart Disease of Young Adults.**

HENRY I. RUSSEK, F.A.C.P., Staten Island, N. Y.
Consultant in Cardiovascular Research, U. S. Public Health Service Hospital.

3:45 **Syndrome of Extreme Obesity and Hypoventilation Studies on Etiology.**

JACK D. HACKNEY, (Associate), Los Angeles, Calif.
Assistant Professor of Medicine, College of Medical Evangelists.

MILTON G. CRANE, M.D., (by invitation), Los Angeles, Calif.
Assistant Clinical Professor of Medicine, College of Medical Evangelists.

CLARENCE R. COLLIER, M.D., (by invitation), Los Angeles, Calif.
Associate Professor of Physiology, College of Medical Evangelists.

STANLEY N. ROKAW, M.D., (by invitation), Los Angeles, Calif.
Assistant Clinical Professor of Medicine, College of Medical Evangelists.

DONALD E. GRIGGS, F.A.C.P., Los Angeles, Calif.
Clinical Professor of Medicine, College of Medical Evangelists.

4:00 **Fever of Obscure Origin; Value of Exploratory Laparotomy: Report of Seventy Patients.**

J. E. GERACI, F.A.C.P., Rochester, Minn.

D. R. NICHOLS, F.A.C.P., Rochester, Minn.

LYLE WEED, M.D., (by invitation), Rochester, Minn.
Section of Medicine, Mayo Clinic and Mayo Foundation.

4:15 **Bacteremia Due to Coagulase—Positive "Staphylococcus Aureus."**

BURTON A. WAISBREN, (Associate), Milwaukee, Wis.
Assistant Clinical Professor of Medicine, Marquette University School of Medicine.

FRANCOIS M. ABBOUD, M.D., (by invitation), Milwaukee, Wis.
Research Associate, Marquette University School of Medicine.

4:30 **Aerogenosis—The Increasing Seriousness of Bacilluria and Bacteremia Due to Aerobacter Aerogenes.**

HARRY SENECA, F.A.C.P., New York, N. Y.

J. K. LATTIMER, F.A.C.S., (by invitation), New York, N. Y.
Department of Urology, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital.

4:45 **Recent Developments in Antibiotic Therapy.**

LOWELL A. RANTZ, F.A.C.P., San Francisco, Calif.
Professor of Medicine, Stanford University School of Medicine.

5:00 **ADJOURNMENT.**

Thursday Evening, April 23, 1959

7:00 o'Clock

Normandie Lounge, Conrad Hilton Hotel

GRATIS COCKTAIL PARTY

(for those holding dinner tickets)

8:00 o'Clock

Grand Ballroom, Conrad Hilton Hotel

THE ANNUAL BANQUET OF THE COLLEGE

Toastmaster

ELIOT E. FOLTZ, F.A.C.P., Winnetka, Ill.

CELEBRITY SHOW

Procure tickets at the Registration Bureau, Conrad Hilton Hotel, before 3.00 P.M., Wednesday. Tickets will be assigned by tables and those wishing to sit together must apply together or on a single application.

CLINICAL SESSION A–5

Grand Ballroom, Conrad Hilton Hotel

Friday Afternoon, April 24, 1959

Presiding Officer

WRIGHT ADAMS, F.A.C.P., Chicago, Ill.

Governor, A.C.P.

P.M.

2:00 **Carotid Artery Compression in Cerebrovascular Insufficiency States; The Influence of Head Position.**

JAMES F. TOOLE, M.D., (by invitation), Philadelphia, Pa.
Instructor in Neurology, University of Pennsylvania School of Medicine.

S. DONALD WEEKS, (by invitation), Philadelphia, Pa.
EEG Technician, Department of Neurology, Hospital of the University of Pennsylvania.

2:15 **The Medical Aspects of Cerebrovascular Disease.**

C. H. MILLIKAN, F.A.C.P., Rochester, Minn.
Section of Neurology, Mayo Clinic and Mayo Foundation.

2:35 **Atherosclerotic Occlusive Disease causing Cerebral Arterial Insufficiency. Surgical Considerations.**

MICHAEL E. De BAKEY, F.A.C.S., (by invitation), Houston, Tex.
Professor of Surgery, Baylor University College of Medicine.

E. STANLEY CRAWFORD, F.A.C.S., (by invitation), Houston, Tex.
Assistant Professor of Surgery, Baylor University College of Medicine.
WILLIAM S. FIELDS, M.D., (by invitation), Houston, Tex.
Professor of Neurology, Baylor University College of Medicine.

3:00 **Diagnosis of Chronic Occlusive Arterial Disease Involving the Aorta and Iliac Arteries.**
EDGAR A. HINES, JR., F.A.C.P., Rochester, Minn.
Professor of Medicine, University of Minnesota (Mayo Foundation).

3:15 **Surgical Aspects of Occlusive Disease of Aorta and Iliac Arteries.**
ALFRED W. HUMPHRIES, F.A.C.S., (by invitation), Cleveland Ohio.
Assistant Professor of Vascular Surgery, Frank E. Bunts Educational Institute, Cleveland Clinic Foundation.

3:30 **ADJOURNMENT.**

CLINICAL SESSION B-1

Blackstone Theatre

Monday Afternoon, April 20, 1959

Presiding Officer
HOWARD P. LEWIS, F.A.C.P., Portland, Ore.
President-Elect

P.M.

2:40 **The Internist's Responsibility in Open Heart Surgery.**
PAUL WINCHELL, (Associate), Minneapolis, Minn.
Assistant Professor, Department of Medicine, University of Minnesota Medical School.

2:55 **Postmitral Commissurotomy Syndrome: Four-Year Clinical Pathologic and Serologic Study and Its Relation to Restenosis.**
PHILIP LISAN, M.D., (by invitation), Philadelphia, Pa.
Instructor, Department of Medicine, Hahnemann Medical College and Hospital of Philadelphia.
WILLIAM LIKOFF, F.A.C.P., Philadelphia, Pa.
Associate Professor of Medicine, Hahnemann Medical College and Hospital of Philadelphia; Cardiologist to the Bailey Thoracic Clinic.
ATTILIO REALE, M.D., (by invitation), Rome, Italy.
Cardiologist, University of Rome.

3:10 **The Prevention and Management of Abnormal Bleeding Following Open Heart Surgery.**
HERBERT A. PERKINS, M.D., (by invitation), St. Louis, Mo.
Assistant Professor of Medicine, Washington University School of Medicine; Hematologist, Jewish Hospital (formerly Assistant Clinical Professor of Medicine, Stanford University School of Medicine).
JOHN J. OSBORN, M.D., (by invitation), San Francisco, Calif.
Associate Professor of Pediatrics, Stanford University School of Medicine.

FRANK GERBODE, F.A.C.S., (by invitation), San Francisco, Calif.
Associate Professor of Surgery, Stanford University School of Medicine.

3:25 **Severe Aortic Stenosis: Evaluation by Clinical and Physiological Criteria and Results of Surgical Treatment.**

LAURENCE B. ELLIS, F.A.C.P., Boston, Mass.
Associate Clinical Professor of Medicine, Harvard Medical School.

WALTER H. ABELMANN, (Associate), Boston, Mass.
Assistant Professor of Medicine, Harvard Medical School.

3:40 **Combined Mitral and Aortic Stenosis: Clinical and Hemodynamic Features.**

J. F. URICCHIO, (Associate), Philadelphia, Pa.
Assistant Professor of Medicine, Hahnemann Medical College and Hospital of Philadelphia; Cardiologist to the Bailey Thoracic Clinic.

HARRY GOLDBERG, F.A.C.P., Philadelphia, Pa.
Assistant Professor of Medicine and Director of Brith Sholem Laboratory, Hahnemann Medical College and Hospital.

LAMBERTO BENTIVOGLIO, M.D., (by invitation), Philadelphia, Pa.
Assistant Director, Brith Sholem Laboratory, Hahnemann Medical College and Hospital.

3:55 **The Natural History of Intermittent Claudication.**

RAYMOND PENNEYS, M.D., (by invitation), Philadelphia, Pa.
Instructor in Medicine, University of Pennsylvania School of Medicine; Vascular Consultant, Sidney Hillman Medical Center of Philadelphia; Chief, Peripheral Vascular Section, Philadelphia General Hospital.

ORVILLE HORWITZ, F.A.C.P., Philadelphia, Pa.
Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine.

4:10 **The Normal Systolic Murmur.**

DALE GROOM, F.A.C.P., Charleston, S. C.
Assistant Professor of Medicine, Medical College of South Carolina.

WADDY CHAPMAN, M.D., (by invitation), Greenville, S. C.
Intern, Greenville General Hospital.

ANNE BASS, M.D., (by invitation), Charleston, S. C.
Assistant Resident, Obstetrics and Gynecology, Medical College of South Carolina.

YRO T. SIHVONEN, M.S., (by invitation), Detroit, Mich.
Physicist, General Motors Research Staff, General Motors Corporation, Detroit, Mich.

WOFFORD W. FRANCIS, (by invitation), Charleston, S. C.
Electronics Technician, Medical College of South Carolina.

4:25 **Physiologic and Biochemical Aspects of the Disordered Coronary Circulation.**

RICHARD GORLIN, (Associate), Boston, Mass.
Associate in Medicine, Harvard Medical School; Associate in Medicine, Peter Bent Brigham Hospital.

NORMAN BRACHFELD, M.D., (by invitation), Boston, Mass.
Research Fellow in Medicine, Harvard Medical School.

JOSEPH V. MESSER, M.D., (by invitation), Boston, Mass.
Research Fellow in Medicine, Harvard Medical School.

JOHN D. TURNER, M.D., (by invitation), Boston, Mass.
Research Fellow in Medicine, Harvard Medical School.

4:40 **An Internist's Appraisal of Surgical Procedures for Angina Pectoris.**

WRIGHT ADAMS, F.A.C.P., Chicago, Ill.
Professor and Chairman, Department of Medicine, The University of Chicago, The School of Medicine.

FAUSTO TANZI, M.D., (by invitation), Chicago, Ill.
Assistant Professor, Department of Medicine, The University of Chicago, The School of Medicine.

CLINICAL SESSION B-2

Blackstone Theatre

Tuesday Afternoon, April 21, 1959

Presiding Officer

THOMAS M. McMILLAN, F.A.C.P., Philadelphia, Pa.
Second Vice President

P.M.

2:00 **Serial Studies of Renal Function During Pregnancy Complicated by Intercapillary Glomerulosclerosis.**

ETHAN A. H. SIMS, F.A.C.P., Burlington, Vt.
Associate Professor of Medicine and of Clinical Biochemistry, University of Vermont College of Medicine.

2:15 **The Pathologic Physiology of Chronic Bright's Disease: A Unified Concept.**

NEAL S. BRICKER, M.D., (by invitation), St. Louis, Mo.
Assistant Professor of Medicine and Preventive Medicine, Washington University School of Medicine.

2:30 **Unilateral Renal Disease as a Cause of Hypertension—Its Detection by Ureteral Catheterization Studies.**

THOMAS B. CONNOR, M.D., (by invitation), Baltimore, Md.
Associate Professor of Medicine, University of Maryland School of Medicine.

MORGAN BERTHRONG, M.D., (by invitation), Colorado Springs, Colo.
Department of Pathology, Glockner-Penrose Hospital.

WILLIAM C. THOMAS, JR., (Associate), Gainesville, Fla.
Assistant Professor of Medicine, University of Florida College of Medicine.

JOHN E. HOWARD, M.D., (by invitation), Baltimore, Md.
Associate Professor of Medicine, Johns Hopkins University School of Medicine.

2:45 **The Natural History of Glomerular Diseases as Revealed by Serial Histologic and Immunologic Observations.**

DAVID P. EARLE, F.A.C.P., Chicago, Ill.
Professor of Medicine, Northwestern University Medical School.

ROBERT B. JENNINGS, M.D., (by invitation), Chicago, Ill.
Assistant Professor of Pathology, Northwestern University Medical School.

3:00 **Diagnosis and Treatment of Renal Hypertension.**

IRVINE H. PAGE, F.A.C.P., Cleveland, Ohio.
Professor of Medicine, Frank E. Bunts Educational Institute, and Director of Research, Cleveland Clinic Foundation.

HARRIET P. DUSTAN, M.D., (by invitation), Cleveland, Ohio.
Staff Member, Cleveland Clinic.

3:15 **Surfeit and Deficit of Salt.**

MAURICE B. STRAUSS, F.A.C.P., Boston, Mass.
Chief of Medical Service, Boston Veterans Administration Hospital.

EZRA LAMDIN, M.D., (by invitation), Boston, Mass.
Clinical Investigator, Medical Service, Boston Veterans Administration Hospital.

W. PIERCE SMITH, M.D., (by invitation), Boston, Mass.
Formerly Resident in Medicine, Boston Veterans Administration Hospital.

DANIEL J. BLEIFER, M.D., (by invitation), Boston, Mass.
Formerly Staff Physician, Boston Veterans Administration Hospital.

3:30 **INTERMISSION.**

Presiding Officer

THOMAS M. DURANT, F.A.C.P., Philadelphia, Pa.

Treasurer

4:00 **Familial Recurring Polyserositis: A Disease Entity.**

ROBERT J. PRIEST, (Associate), Detroit, Mich.
Associate Physician, Division of Gastroenterology, Henry Ford Hospital.

ROBERT K. NIXON, (Associate), Detroit, Mich.
Associate Physician, Division of General Medicine, Henry Ford Hospital.

4:15 **A Comparative Study of Some Recent Serologic Tests for Rheumatoid Arthritis.**

WILLIAM M. MIKKELSEN, M.D., (by invitation), Ann Arbor, Mich.
Assistant Professor, Department of Internal Medicine, University of Michigan Medical School.

IVAN F. DUFF, F.A.C.P., Ann Arbor, Mich.
Associate Professor, Department of Internal Medicine, University of Michigan Medical School.

LEROY GOODSON, (by invitation), Ann Arbor, Mich.
Medical Student, University of Michigan Medical School.

WILLIAM H. COULTER, (by invitation), Ann Arbor, Mich.
Medical Student, University of Michigan Medical School.

C. HERTZ, (by invitation), Ann Arbor, Mich.
Bacteriologist, Veterans Administration Hospital.

4:30 **Some Interrelations Between Sleep and Disease.**

EUGENE D. ROBIN, M.D., (by invitation), Boston, Mass.
Associate in Medicine, Harvard Medical School; Associate in Medicine, Peter Bent Brigham Hospital.

4:45 **Effectiveness of Peritoneal Dialysis in Various Clinical Situations.**

MORTON H. MAXWELL, M.D., (by invitation), Los Angeles, Calif.
Associate Clinical Professor of Medicine, University of California School of Medicine at Los Angeles.

ROBERT E. ROCKNEY, M.D., (by invitation), Los Angeles, Calif.
Clinical Instructor in Medicine, University of California School of Medicine at Los Angeles.

CHARLES R. KLEEMAN, M.D., (by invitation), Los Angeles, Calif.
Chief, Metabolic Service, Wadsworth General Hospital, Veterans Administration Center.

5:00 **ADJOURNMENT.**

CLINICAL SESSION B-3

Williford Room, Conrad Hilton Hotel

Wednesday Afternoon, April 22, 1959

Presiding Officer

PHILIP S. HENCH, F.A.C.P., Rochester, Minn.
Regent, A.C.P.

P.M.

2:00 **The Lilly Lecture: Changing Views on Heart Failure.**

JOHN McMICHAEL, M.D., F.R.C.P., F.R.S., (by invitation), London, England.
Professor of Medicine, University of London; Director, Department of Medicine, Postgraduate Medical School of London.

2:20 **Cardiac Vagal Deficiency Caused by Lack of Physical Exercise.**

WILHELM RAAB, F.A.C.P., Burlington, Vt.
Professor of Experimental Medicine, University of Vermont College of Medicine.

EIICHI KIMURA, M.D., (by invitation), Tokyo, Japan.
Professor of Medicine, Japan Medical College.

PAULO de PAULA SILVA, M.D., (by invitation), Sao Paulo, Brazil.
Associate in Medicine, Medical Clinic, University of Sao Paulo Faculty of Medicine.

HANS MARCHET, M.D., (by invitation), Innsbruck, Austria.
Research Associate, Medical Clinic, University of Innsbruck.

YVONNE K. STARCHESKA, M.D., (by invitation), Burlington, Vt.
Research Assistant, Cardiovascular Research Unit, University of Vermont College of Medicine.

2:35 **Adrenal Factors in Hypertension.**

WILLIAM A. JEFFERS, F.A.C.P., Philadelphia, Pa.
Associate Professor of Medicine, University of Pennsylvania School of Medicine.

DAVID Y. COOPER, M.D., (by invitation), Philadelphia, Pa.
Associate in Surgery, University of Pennsylvania School of Medicine.

ALFRED M. SELLERS, (Associate), Philadelphia, Pa.
Associate in Medicine, University of Pennsylvania School of Medicine.

WILLIAM S. BLAKEMORE, F.A.C.S., (by invitation), Philadelphia, Pa.
Assistant Professor of Surgery, University of Pennsylvania School of Medicine.

CHARLES C. WOLFERTH, F.A.C.P., Philadelphia, Pa.
Emeritus Professor of Medicine, University of Pennsylvania School of Medicine.

2:50 **Summary of Clinical and Pathological Findings in a Series of Cases of Subendocardial Fibrosis.**

WALTER NEWMAN, F.A.C.P., Bronx, N. Y.
Assistant Chief, Cardiac Section, Bronx Veterans Administration Hospital.

ROBERT F. GOMPRECHT, M.D., (by invitation), Bronx, N. Y.
Assistant Chief, Cardiac Section, Bronx Veterans Administration Hospital.

CHARLES A. R. CONNOR, F.A.C.P., Bronx, N. Y.
Attending Physician, Bronx Veterans Administration Hospital.

BENJAMIN S. GORDON, (Associate), Bronx, N. Y.
Chief, Pathology Service, Bronx Veterans Administration Hospital.

3:05 **A Clinical and Physiological Evaluation of Hyperventilation Mechanisms.**

BERNARD I. LEWIS, F.A.C.P., Palo Alto, Calif.
Assistant Clinical Professor of Medicine, Stanford University School of Medicine; Internist, Palo Alto Medical Clinic.

3:20 **INTERMISSION.**

Presiding Officer

CHESTER M. JONES, M.A.C.P., Boston, Mass.

Regent, A.C.P.

3:45 **Aseptic Meningitis: Including EEG Abnormalities.**

ROBERT B. ABINGTON, M.D., (by invitation), Honolulu, Hawaii.
Captain, (MC), U. S. Army; Chief Resident, Department of Medicine, Tripler Army Hospital.

WILBUR C. BERRY, F.A.C.P., Tacoma, Wash.
Colonel, (MC), U. S. Army; Chief, Department of Medicine, Madigan Army Hospital.

FREDERICK S. ARMSTRONG, M.D., (by invitation), Washington, D. C.
Captain, (MC), U. S. Army; Senior Resident in Internal Medicine, Walter Reed Army Hospital.

4:00 Urine Cation Excretion in Neuropsychiatric Illness.

HENRY A. PETERS, F.A.C.P., Madison, Wis.
Associate Professor of Neurology, University of Wisconsin Medical School.

4:15 Observations on the Effects of Alkylating Agents in Human Neoplastic Disease.

BYRON E. HALL, F.A.C.P., San Francisco, Calif.
Associate Clinical Professor of Medicine, Stanford University School of Medicine.

FORREST M. WILLETT, F.A.C.P., San Francisco, Calif.
Associate Clinical Professor of Medicine, Stanford University School of Medicine; Chief of Medicine, Veterans Administration Hospital.

DONALD R. HALES, M.D., (by invitation), San Francisco, Calif.
Instructor in Medicine, Stanford University School of Medicine.

4:30 Intrathoracic Manifestations of Malignant Lymphomatous Disease.

JOHN H. FELTS, (Associate), Winston-Salem, N. C.
Assistant in Internal Medicine, Bowman Gray School of Medicine of Wake Forest College.

ARCHIE H. CARMICHAEL, M.D., (by invitation), Winston-Salem, N. C.
Assistant Resident in Medicine, Bowman Gray School of Medicine of Wake Forest College and North Carolina Baptist Hospital.

DAMON D. BLAKE, M.D., (by invitation), Winston-Salem, N. C.
Instructor in Radiology, Bowman Gray School of Medicine of Wake Forest College.

4:45 Some Unusual Syndromes Associated with Neoplastic Disease.

G. LENNARD GOLD, M.D., (by invitation), Washington, D. C.
Clinical Instructor in Medicine, Georgetown University School of Medicine; Assistant Director, Cancer Chemotherapy Research Program (Georgetown University Medical Division), District of Columbia General Hospital.

BRUCE I. SHNIDER, (Associate), Washington, D. C.
Assistant Professor of Medicine, Georgetown University School of Medicine; Chief Visiting Physician and Director, Cancer Chemotherapy Research Program (Georgetown University Medical Division), District of Columbia General Hospital.

5:00 ADJOURNMENT.

CLINICAL SESSION B-4

Blackstone Theatre

Thursday Afternoon, April 23, 1959

Presiding Officer

THOMAS FINDLAY, F.A.C.P., Augusta, Ga.

Regent, A.C.P.

P.M.

2:45 **Oral Antidiabetic Therapy.**

ROBERT H. WILLIAMS, F.A.C.P., Seattle, Wash.
Professor of Medicine, University of Washington School of Medicine.

3:05 **Paradoxical Lengthening of Muscle Contraction in Hypothyroid Patients Given Small Doses of Liothyronine, Thyroxine, and Desiccated Thyroid.**

ARTHUR S. WEISSBEIN, M.D., (by invitation), Fort Sam Houston, Tex.
Captain, (MC), U. S. Army; Senior Resident, Department of Medicine, Brooke Army Hospital.

JOHN D. LAWSON, M.D., (by invitation), Fort Sam Houston, Tex.
Major, (MC), U. S. Army; formerly Senior Resident, Department of Medicine, Brooke Army Hospital.

3:20 **A Clinical Study of Thyroid Storm.**

SHELDON S. WALDSTEIN, (Associate), Chicago, Ill.
Assistant Professor of Medicine, Northwestern University Medical School; Attending Physician, Cook County Hospital.

SHELDON J. SLODKI, M.D., (by invitation), Chicago, Ill.
Resident in Medicine, Cook County Hospital.

G. IRENE KAGANIEC, M.D., (by invitation), Chicago, Ill.
Associate in Endocrinology, Cook County Hospital.

DAVID BRONSKY, (Associate), Chicago, Ill.
Instructor in Medicine, University of Illinois College of Medicine; Attending Physician, Cook County Hospital.

3:35 **Neurologic Complications of Myxedema: Convulsions.**

EDWIN C. EVANS, (Associate), Atlanta, Ga.
Associate in Medicine, Emory University School of Medicine.

3:45 **Neurologic Complications of Myxedema: Peripheral Neuropathy.**

LAMAR E. CREVASSE, M.D., (by invitation), Gainesville, Fla.
Instructor in Medicine, University of Florida College of Medicine.

R. BRUCE LOGUE, F.A.C.P., Atlanta, Ga.
Professor of Medicine, Emory University School of Medicine.

3:55 **A Consideration of Acromegaly and the Newer Methods of Evaluating Pituitary Growth Hormone Secretion.**

WILLIAM H. DAUGHADAY, M.D., (by invitation), St. Louis, Mo.
Associate Professor of Medicine and Director of Metabolism Division, Washington University School of Medicine.

4:15 **Cushing's Syndrome: An Analysis of 50 Personally Observed Cases.**

J. LESTER GABRILOVE, F.A.C.P., New York, N. Y.
Clinical Assistant Professor of Medicine, State University of New York College of Medicine at New York City; Assistant Attending Physician, Mount Sinai Hospital.

LOUIS J. SOFFER, F.A.C.P., New York, N. Y.
Clinical Professor of Medicine, State University of New York College of Medicine at New York City; Attending Physician, Mount Sinai Hospital.

ANGELO IANNACCONE, M.D., (by invitation), New York, N. Y.
Research Fellow, Mount Sinai Hospital.

4:30 **On Incidence and Causality of Senile Osteoporosis.**
RICHMOND W. SMITH, JR., (Associate), Detroit, Mich.
RAYMOND C. MELLINGER, M.D., (by invitation), Detroit, Mich.
Division of Endocrinology, Henry Ford Hospital.

4:45 **ADJOURNMENT.**

BASIC SCIENCE SESSIONS

Eighth Street Theatre

FIRST BASIC SCIENCE SESSION

Monday Afternoon, April 20, 1959

Presiding Officer

ROBERT H. WILLIAMS, F.A.C.P., Seattle, Wash.

Chairman, Basic Science Sessions

P.M.

2:40 **Ventricular Depolarization and the QRS Complex.**
ALLEN M. SCHER, Ph.D., (by invitation), Seattle, Wash.
Associate Professor of Physiology and Biophysics, University of Washington School of Medicine.
ROBERT V. ERICKSON, M.D., (by invitation), Fort Knox, Ky.
Captain, (MC), U. S. Army; Army Medical Research Laboratory.
ROLFE A. BECKER, M.D., (by invitation), Minneapolis, Minn.
Resident, Department of Ophthalmology, Veterans Administration Hospital.

3:05 **Cardiac Control in Intact Unanesthetized Dogs.**
ROBERT F. RUSHMER, M.D., (by invitation), Seattle, Wash.
Professor of Physiology and Biophysics, University of Washington School of Medicine.

3:30 **Plasma Catechol Amine Response to Acute Postural Change; Physiological and Pharmacological Observations.**
ROGER B. HICKLER, (Associate), Boston, Mass.
Instructor in Medicine, Harvard Medical School.
ROE E. WELLS, JR., (Associate), Boston, Mass.
Clinical Associate in Medicine, Harvard Medical School.
H. RICHARD TYLER, M.D., (by invitation), Boston, Mass.
Instructor in Neurology, Harvard Medical School.
JAMES T. HAMLIN, III, M.D., (by invitation), Boston, Mass.
Research Fellow in Medicine, Harvard Medical School.

3:45 **Electrolyte Transport Across Nephron Wall as Localized by Stop Flow Analysis.**

WALTER S. WILDE, Ph.D., (by invitation), Ann Arbor, Mich.
Professor of Physiology, University of Michigan Medical School.

RICHARD L. MALVIN, Ph.D., (by invitation), Ann Arbor, Mich.
Instructor in Physiology, University of Michigan Medical School.

LAWRENCE P. SULLIVAN, M.S., (by invitation), Ann Arbor, Mich.
Teaching Assistant, University of Michigan Medical School.

ARTHUR J. VANDER, B.S., (by invitation), Ann Arbor, Mich.

4:00 **Physiology of Renal Juxtaglomerular Cells.**

LOUIS TOBIAN, M.D., (by invitation), Minneapolis, Minn.
Associate Professor of Medicine, University of Minnesota Medical School.

4:15 **Proliferative Disorders of Bone Marrow Studied with Tritiated Thymidine.**

VICTOR P. BOND, M.D., (by invitation), Upton, N. Y.
Head, Division of Microbiology, Medical Department, Brookhaven National Laboratory.

E. P. CRONKITE, M.D., (by invitation), Upton, N. Y.
Head, Division of Experimental Pathology, Medical Department, Brookhaven National Laboratory.

T. M. FLIEDNER, M.D., (by invitation), Upton, N. Y.
Medical Associate, Medical Research Center, Brookhaven National Laboratory.

J. R. RUBINI, M.D., (by invitation), Upton, N. Y.
Medical Associate, Medical Research Center, Brookhaven National Laboratory.

4:30 **Immunohistochemical Studies of Connective Tissue Diseases.**

J. J. VAZQUEZ, M.D., (by invitation), Pittsburgh, Pa.
Assistant Professor of Pathology, University of Pittsburgh School of Medicine.

4:50 **ADJOURNMENT.**

SECOND BASIC SCIENCE SESSION

Eighth Street Theatre

Tuesday Afternoon, April 21, 1959

Presiding Officer

ROBERT H. WILLIAMS, F.A.C.P., Seattle, Wash.

P.M.

2:00 **Current Ideas of the Mechanism of Protein Synthesis.**

PAUL BERG, Ph.D., (by invitation), St. Louis, Mo.
Associate Professor of Microbiology, Washington University School of Medicine.

2:15 **Biosynthesis of Desoxyribonucleic Acid.**

ARTHUR KORNBERG, M.D., (by invitation), St. Louis, Mo.
Professor and Head of the Department of Microbiology, Washington University School of Medicine.

2:40 **Biochemistry of Macroglobulins.**
HAROLD F. DEUTSCH, Ph.D., (by invitation), Madison Wis.
Professor of Physiology Chemistry, University of Wisconsin Medical School.

3:00 **Functions of Norepinephrine and Serotonin in the Brain.**
BERNARD B. BRODIE, Ph.D., (by invitation), Bethesda, Md.
Laboratory Chief, Laboratory of Chemical Pharmacology, National Heart Institute.

3:30 **INTERMISSION.**

4:00 **Interaction of Metals with Biological Systems.**
BERT L. VALLEE, M.D., (by invitation), Boston, Mass.
Assistant Professor of Medicine and Tutor in Medical Science, Harvard Medical School.

4:40 **Metals and Metabolism.**
WARREN E. C. WACKER, M.D., (by invitation), Boston, Mass.
Instructor in Medicine, Harvard Medical School.

5:00 **ADJOURNMENT.**

THIRD BASIC SCIENCE SESSION

Eighth Street Theatre

Wednesday Afternoon, April 22, 1959

Presiding Officer

ROBERT H. WILLIAMS, F.A.C.P., Seattle, Wash.

P.M.

2:00 **Biosynthesis of Mucopolysaccharides.**
ALBERT DORFMAN, M.D., (by invitation), Chicago, Ill.
Associate Professor of Pediatrics, The University of Chicago, The School of Medicine.
ALVIN MARKOVITZ, Ph.D., (by invitation), Chicago, Ill.
Research Associate, LaRabida Institute, and Instructor in Microbiology, The University of Chicago.
J. A. CIFONELLI, Ph.D., (by invitation), Chicago, Ill.
Research Associate, LaRabida Institute, and Assistant Professor of Biochemistry, The University of Chicago.

2:20 **Collagen Formation.**
JEROME GROSS, M.D., (by invitation), Boston, Mass.
Assistant Professor of Medicine, Harvard Medical School.

2:50 **Unusual "Antibodies" in Certain of the Collagen Disorders.**
HENRY G. KUNKEL, M.D., (by invitation), New York, N. Y.
Member and Professor, Rockefeller Institute.
HALSTED R. HOLMAN, M.D., (by invitation), New York, N. Y.
Assistant Professor, Rockefeller Institute.
HELMUTH DEICHER, M.D., (by invitation), New York, N. Y.
Research Associate, Rockefeller Institute.

3:10 **Physiologic Role of Acetyl Cholinesterase.**

GEORGE B. KOELLE, M.D., (by invitation), Philadelphia, Pa.
Professor of Pharmacology and Dean, University of Pennsylvania Graduate School of Medicine.

3:35 **INTERMISSION.**

4:00 **Pathogenesis of Atherosclerosis.**

ROBERT W. WISSLER, M.D., (by invitation), Chicago, Ill.
Professor and Chairman, Department of Pathology, The University of Chicago, The School of Medicine.

4:20 **Experimental Laennec's Cirrhosis in Monkeys.**

GEORGE F. WILGRAM, M.D., (by invitation), Chicago, Ill.
Assistant Professor, Ben May Laboratory for Cancer Research, The University of Chicago, The School of Medicine.

4:35 **Mouse Polyoma Virus Infection.**

WALLACE P. ROWE, M.D., (by invitation), Bethesda, Md.
Chief, Oncolytic and Oncogenic Virus Unit, Viral and Rickettsial Section. Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, U. S. Public Health Service.

JANET W. HARTLEY, Ph.D., (by invitation), Bethesda, Md.
Medical Bacteriologist, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, U. S. Public Health Service.

ROBERT J. HUEBNER, M.D. (by invitation), Bethesda, Md.
Chief, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, U. S. Public Health Service.

4:50 **ADJOURNMENT.**

FOURTH BASIC SCIENCE SESSION

Eighth Street Theatre

Thursday Afternoon, April 23, 1959

Presiding Officer

ROBERT H. WILLIAMS, F.A.C.P., Seattle, Wash.

P.M.

2:45 **Effect of Hormones on Fat Mobilization.**

FRANK L. ENGEL, (Associate), Durham, N. C.
Professor of Medicine, Duke University School of Medicine.

J. EARLE WHITE, M.D., (by invitation), Durham, N. C.
American Diabetes Association Research Fellow.

ENRIQUE LOPEZ, M.D., (by invitation), Durham, N. C.
Eli Lilly Traveling Fellow, Santiaga, Chile.

JOHN V. VERNER, M.D., (by invitation), Durham, N. C.
American College of Physicians Research Fellow.

3:05 **Adipose Tissue Metabolism.**

GEORGE F. CAHILL, JR., M.D., (by invitation), Boston, Mass.
Instructor in Medicine, Harvard Medical School.

ALBERT E. RENOLD, M.D., (by invitation), Boston, Mass.
Associate in Medicine, Harvard Medical School.

GEORGE W. THORN, F.A.C.P., Boston, Mass.
Hersey Professor of the Theory and Practice of Physic, Harvard Medical School.

3:25 **The Lipid Mobilizer Hormone of the Neurohypophysis.**

CHRIS J. D. ZARAFONETIS, F.A.C.P., Philadelphia, Pa.
Clinical Professor of Medicine, Temple University School of Medicine.

JOSEPH SEIFTER, M.D., (by invitation), Radnor, Pa.
Medical Director, Wyeth Institute for Medical Research.

DAVID H. BAEDER, Ph.D., (by invitation), Radnor, Pa.
Pharmacologist, Wyeth Institute for Medical Research.

JOHN P. KALAS, M.D., (by invitation), Philadelphia, Pa.
Research Fellow, Department of Medicine, Temple University School of Medicine.

3:40 **Adaptation of the Fat-forming Apparatus of Liver Cells.**

JAY TEPPERMAN, M.D., (by invitation), Syracuse, N. Y.
Professor of Experimental Medicine, State University of New York College of Medicine in Syracuse.

HELEN M. TEPPERMAN, Ph.D., (by invitation), Syracuse, N. Y.
Assistant Professor of Pharmacology, State University of New York College of Medicine in Syracuse.

4:00 **Some Aspects of the Metabolism of Pentose Sugars in Man.**

IRVIN C. PLOUGH, F.A.C.P., Denver, Colo.
Lieutenant Colonel, (MC), U. S. Army; Chief, Metabolic Division, U. S. Army Medical Research and Nutrition Laboratory, Fitzsimons Army Hospital.

EDWIN L. BIERMAN, M.D., (by invitation), Denver, Colo.
Captain, (MC), U. S. Army; Staff, Metabolic Division, U. S. Army Medical Research and Nutrition Laboratory, Fitzsimons Army Hospital.

EUGENE M. BAKER, Ph.D., (by invitation), Denver, Colo.
Captain, (MSC), U. S. Army; Staff, Metabolic Division, U. S. Army Medical Research and Nutrition Laboratory, Fitzsimons Army Hospital.

4:15 **Dietary Production of Myocardial Infarcts in Animals.**

W. STANLEY HARTROFT, M.D., (by invitation), St. Louis, Mo.
Professor of Pathology and Head of the Department, Washington University School of Medicine.

4:40 **Cholesterol Exchange in the Intestine in Normal and Abnormal Subjects.**

SAMUEL H. CHENG, M.D., (by invitation), Louisville, Ky.
Assistant Professor of Medicine, University of Louisville School of Medicine.

MALCOLM M. STANLEY, (Associate), Louisville, Ky.
Professor of Experimental Medicine, University of Louisville School of Medicine.

4:55 **ADJOURNMENT.**

FIFTH BASIC SCIENCE SESSION

Eighth Street Theatre

Friday Afternoon, April 24, 1959

Presiding Officer

ROBERT H. WILLIAMS, F.A.C.P., Seattle, Wash.

P.M.

2:00 **Metabolism and Mode of Action of Steroid Hormones.**

PAUL TALALAY, M.D., (by invitation), Chicago, Ill.
Associate Professor of Biochemistry, Ben May Laboratory for Cancer Research, The University of Chicago, The School of Medicine.

2:20 **Steroid Action in Isolated Smooth Muscle.**

ALLAN D. BASS, SR., F.A.C.P., Nashville, Tenn.
Professor of Pharmacology and Chairman of the Department, Vanderbilt University School of Medicine.

JAMES SETLIFF, B.A., (by invitation), Nashville, Tenn.
Research Associate in Pharmacology, Vanderbilt University School of Medicine.

2:35 **Endocrine Control of Cellular Transfer of Amino Acids.**

HALVOR N. CHRISTENSEN, Ph.D., (by invitation), Ann Arbor, Mich.
Professor of Biological Chemistry, University of Michigan Medical School.

THOMAS R. RIGGS, Ph.D., (by invitation), Ann Arbor, Mich.
Assistant Professor of Biological Chemistry, University of Michigan Medical School.

DALE OXENDER, Ph.D., (by invitation), Ann Arbor, Mich.
Research Associate in Biological Chemistry, University of Michigan Medical School.

2:50 **Mechanisms Controlling the Secretion of Aldosterone.**

FREDERIC C. BARTTER, M.D., (by invitation), Bethesda, Md.
Chief, Section of Clinical Endocrinology, National Institutes of Health.

JOHN R. GILL, M.D., (by invitation), Bethesda, Md.
Staff Member, Section of Clinical Endocrinology, National Institutes of Health.

DONALD S. GANN, M.D., (by invitation), Bethesda, Md.
Staff Member, Section of Clinical Endocrinology, National Institutes of Health.

3:05 **Measurement of Energy and Material Balance by Use of Doubly-labeled Water.**

NATHAN LIFSON, M.D., (by invitation), Minneapolis, Minn.
Professor of Physiology, University of Minnesota Medical School.

J. S. LEE, Ph.D., (by invitation), Minneapolis, Minn.
Research Associate in Physiology, University of Minnesota Medical School.

3:20 **Autoimmunization in Thyroiditis.**

ERNEST WITEBSKY, M.D., (by invitation), Buffalo, N. Y.
Professor and Head of the Department of Bacteriology and Immunology, University of Buffalo School of Medicine.

3:35 **ADJOURNMENT.**

CLINICAL INVESTIGATION SESSIONS

Waldorf Room, Conrad Hilton Hotel

FIRST CLINICAL INVESTIGATION SESSION

Monday, April 20, 1959

Presiding Officer

CARL V. MOORE, F.A.C.P., St. Louis, Mo.
Governor, A.C.P.

P.M.

2:45 **Factors Controlling Hemopoiesis.**

JAMES W. LINMAN, (Associate), Chicago, Ill.
Assistant Professor of Medicine, Northwestern University Medical School; Chief, Hematology Section, Veterans Administration Research Hospital.

FRANK H. BETHELL, F.A.C.P., Ann Arbor, Mich.
Professor of Internal Medicine, University of Michigan Medical School; Director, Thomas Henry Simpson Memorial Institute for Medical Research.

3:00 **Characterization of the Anemia Associated with Chronic Renal Insufficiency.**

ROBERT D. LANGE, (Associate), St. Louis, Mo.
Assistant Professor, Department of Medicine, Washington University School of Medicine; Staff, Veterans Administration Hospital.

NEIL I. GALLAGHER, M.D., (by invitation), St. Louis, Mo.
Resident, Veterans Administration Hospital.

JOHN M. McCARTHY, M.D., (by invitation), St. Louis, Mo.
Staff Physician, Veterans Administration Hospital.

3:15 **Two Varieties of Hemolytic Anemia in Portal Cirrhosis.**

LESLIE ZIEVE, F.A.C.P., Minneapolis, Minn.
Associate Professor of Medicine, University of Minnesota Medical School; Chief, Radioisotope Service, Veterans Administration Hospital.

EARL HILL, (Associate), Minneapolis, Minn.
Clinical Instructor in Medicine, University of Minnesota Medical School; Department of Medicine and Radioisotope Service, Veterans Administration Hospital.

3:30 **The Role of the Dipyrrylmethene (Fuscin) Pigments in Hemoglobin Metabolism.**

A. SIGRID GILBERTSEN, M.D., (by invitation), Minneapolis, Minn.
Instructor in Medicine, University of Minnesota Medical School.

VIOLET HAWKINSON, B.S., (by invitation), Minneapolis, Minn.

CECIL J. WATSON, F.A.C.P., Minneapolis, Minn.
Professor of Medicine and Chairman of the Department, University of Minnesota Medical School.

3:45 **Abnormal Urinary Amino Acid Patterns in Acute Intermittent Porphyria.**

SHERMAN M. MELLINKOFF, (Associate), Los Angeles, Calif.
Associate Professor of Medicine, University of California School of Medicine at Los Angeles.

RICHARD M. HALPERN, M.D., (by invitation), Los Angeles, Calif.
Assistant Clinical Professor of Medicine, University of California School of Medicine at Los Angeles.

MARJORIE FRANKLAND, A.B., (by invitation), Los Angeles, Calif.

MARGARET GREIPEL, A.B., (by invitation), Los Angeles, Calif.

4:00 **Kinetic Aspects of Gastrointestinal Absorption of Cyanocobalamin.**

ALFRED DOSCHERHOLMEN, M.D., (by invitation), Minneapolis, Minn.
Instructor in Medicine, University of Minnesota Medical School; Veterans Administration Clinical Investigator, Veterans Administration Hospital.

PAUL S. HAGEN, F.A.C.P., Minneapolis, Minn.
Associate Professor of Medicine, University of Minnesota Medical School; Chief, Hematology Section, Medical Service, Veterans Administration Hospital.

4:15 **Studies on Blood Platelet Phospholipids.**

AARON J. MARCUS, M.D., (by invitation), New York, N. Y.
Acting Chief, Hematology Section, Veterans Administration Hospital, and Staff, Montefiore Hospital.

THEODORE H. SPAET, M.D., (by invitation), New York, N. Y.
Staff, Veterans Administration Hospital and Montefiore Hospital.

4:30 **DNA-Protein "Sensitivity" in Collagen or Connective Tissue Diseases.**

ARTHUR PERRY HALL, M.D., (by invitation), Boston, Mass.
Assistant in Medicine, Peter Bent Brigham Hospital; Junior Visiting Physician, Robert Breck Brigham Hospital.

WADI A. BARDAWIL, M.D., (by invitation), Boston, Mass.
Assistant Professor of Pathology, Tufts University School of Medicine.

THEODORE B. BAYLES, F.A.C.P., Boston, Mass.
Clinical Associate in Medicine, Harvard Medical School.

4:45 **Titration and Significance of Antinuclear Antibody in Patients with Systemic Lupus Erythematosus and Other Diseases.**

CHARLES W. BAUGH, M.D., (by invitation), Baltimore, Md.
Fellow in Medicine, The Johns Hopkins University School of Medicine.

5:00 **ADJOURNMENT.**

SECOND CLINICAL INVESTIGATION SESSION

Waldorf Room, Conrad Hilton Hotel

Tuesday, April 21, 1959

Presiding Officer

E. HUGH LUCKEY, F.A.C.P., New York, N. Y.

P.M.

2:00 Idiopathic Hypoalbuminemic Syndromes.

THOMAS A. WALDMANN, M.D., (by invitation), Bethesda, Md.
Fellow, American Heart Association, National Cancer Institute, National Institutes of Health.

ROBERT S. GORDON, JR., M.D., (by invitation), Bethesda, Md.
Investigator, National Heart Institute, National Institutes of Health.

2:15 Clinical Implications Derived from a Study of Viral Hepatitis in Mice.

FELIX WROBLEWSKI, F.A.C.P., New York, N. Y.
Assistant Professor of Clinical Medicine, Cornell University Medical College; Assistant Attending Physician, Memorial Center for Cancer and Allied Diseases.

CHARLOTTE FRIEND, Ph.D., (by invitation), New York, N. Y.
Associate, Sloan-Kettering Institute.

MARTIN PODGAINY, B.A., (by invitation), Louisville, Ky.

CARLOS MANSO, M.D., (by invitation), Lisbon, Portugal.
Former Research Fellow, Sloan-Kettering Institute.

2:30 The Serum Bile Acid Ratio in Hepatobiliary Disease.

JAMES B. CAREY, JR., M.D., (by invitation), Minneapolis, Minn.
Assistant Professor of Medicine, University of Minnesota Medical School.

2:45 Patterns of Alkaline Phosphatase Activity as Revealed by Zone Electrophoresis of Serum.

ISADORE N. ROSENBERG, M.D., (by invitation), Boston, Mass.
Assistant Professor of Medicine, Boston University School of Medicine.

3:00 Leucine Aminopeptidase in Cancer of the Pancreas and Liver Disease.

ESTEBAN P. PINEDA, M.D., (by invitation), Boston, Mass.
Research Fellow in Surgery, Harvard Medical School; Research Associate in Surgery, Beth Israel Hospital.

BENJAMIN M. BANKS, M.D., (by invitation), Boston, Mass.
Clinical Associate in Medicine, Harvard Medical School; Associate in Medical Research, Beth Israel Hospital.

JULIUS A. GOLDBARG, M.D., (by invitation), Boston, Mass.
Research Associate in Surgery, Harvard Medical School and Beth Israel Hospital.

ALEXANDER M. RUTENBURG, M.D., (by invitation), Boston, Mass.
Associate in Surgery, Harvard Medical School; Assistant Director of Surgical Research, Beth Israel Hospital.

3:45 Atherosclerosis and Serum Lipids Other than Cholesterol.

DAVID ADLERSBERG, F.A.C.P., New York, N. Y.
Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons; Staff Member, Mount Sinai Hospital.

4:00 Effect of Dietary Protein Deprivation on Serum Lipids and Lipoproteins and their Response to Androgen or Estrogen Administration.

ROBERT H. FURMAN, F.A.C.P., Oklahoma City, Okla.
Associate Professor of Research Medicine, University of Oklahoma School of Medicine; Head of the Cardiovascular Section, Oklahoma Medical Research Foundation.

R. PALMER HOWARD, F.A.C.P., Oklahoma City, Okla.
Associate Professor of Research Medicine, University of Oklahoma School of Medicine; Associate Head, Cardiovascular Section, Oklahoma Medical Research Foundation.

LEONARD N. NORCIA, Ph.D., (by invitation), Oklahoma City, Okla.
Assistant Professor of Biochemistry, University of Oklahoma School of Medicine; Biochemist, Cardiovascular Section, Oklahoma Medical Research Foundation.

4:15 Psychophysiologic Studies of Fat Metabolism.

M. D. BOGDONOFF, M.D., (by invitation), Durham, N. C.
Assistant Professor of Medicine, Duke University School of Medicine.

E. H. ESTES, JR., M.D., (by invitation), Durham, N. C.
Assistant Professor of Medicine, Duke University School of Medicine; Chief of the Medical Service, Veterans Administration Hospital.

W. HARLAN, M.D., (by invitation), Durham, N. C.
Fellow in Medicine, Duke University School of Medicine.

4:30 The Effect of Addition of Chylomicrons from Different Fats on the Fibrinolytic Activity of Epinephrine-stimulated Plasma.

MAURICE SOKOLOW, F.A.C.P., San Francisco, Calif.
Professor of Medicine, University of California School of Medicine.

JOHN W. FARQUHAR, M.D., (by invitation), New York, N. Y.
Research Associate and Assistant Physician to the Hospital of the Rockefeller Institute.

THOMAS C. MERIGAN, M.D., (by invitation), San Francisco, Calif.
Department of Medicine, University of California School of Medicine.

4:45 Circulating Insulin Antagonists in Diabetes Mellitus.

JAMES B. FIELD, M.D., (by invitation), Bethesda, Md.
Senior Investigator, Clinical Endocrinology Branch, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

5:00 ADJOURNMENT.

THIRD CLINICAL INVESTIGATION SESSION

Waldorf Room, Conrad Hilton Hotel

Wednesday, April 22, 1959

Presiding Officer

JACK D. MYERS, F.A.C.P., Pittsburgh, Pa.

P.M.

2:00 **The Countercurrent Hypothesis for Urine Concentration.**

CARL W. GOTTSCHALK, (Associate), Chapel Hill, N. C.
Assistant Professor of Medicine, University of North Carolina School of Medicine; Established Investigator of the American Heart Association.

2:30 **Toxicity of Urea and its Role in the Pathogenesis of the Symptoms of Uremia.**

ARTHUR GROLLMAN, F.A.C.P., Dallas, Tex.
Professor of Experimental Medicine, University of Texas Southwestern Medical School.

EVELYN F. GROLLMAN, (by invitation), Dallas, Tex.

2:45 **Asymptomatic Persistent Proteinuria: Studies by Renal Biopsy.**

VICTOR E. POLLAK, M.B., M.R.C.P. (Edin.), (by invitation), Chicago, Ill.
Research Associate, University of Illinois College of Medicine.

CONRAD L. PIRANI, M.D., (by invitation), Chicago, Ill.
Professor of Pathology, University of Illinois College of Medicine.

ROBERT C. MUEHRCKE, M.D., (by invitation), Chicago, Ill.
Instructor in Medicine, University of Illinois College of Medicine.

ROBERT M. KARK, F.A.C.P., F.R.C.P. (Lond.), Chicago, Ill.
Professor of Medicine, University of Illinois College of Medicine.

3:00 **Abnormalities of the Refractory and Irresponsive Periods of Single Muscle Fibers in Progressive Muscular Dystrophy.**

THOMAS W. FARMER, F.A.C.P., Chapel Hill, N. C.
Professor of Neurologic Medicine, University of North Carolina School of Medicine.

FRITZ BUCHTHAL, M.D., (by invitation), Copenhagen, Denmark.
Director, Institute of Neurophysiology, University of Copenhagen.

PAUL ROSENFALCK, M.Sc., (by invitation), Copenhagen, Denmark.
Institute of Neurophysiology, University of Copenhagen.

3:45 **An Objective Technique as an Aid in the Diagnosis of Acute Pulmonary Embolism.**

EUGENE D. ROBIN, M.D., (by invitation), Boston, Mass.
Associate in Medicine, Harvard Medical School and Peter Bent Brigham Hospital.

DAVID M. TRAVIS, (Associate), Gainesville, Fla.
Assistant Professor of Medicine, University of Florida College of Medicine.

DESMOND G. JULIAN, M.D., (by invitation), Edinburgh, Scotland.
Lecturer in Medicine, Edinburgh University School of Medicine.

CHARLES H. CRUMP, M.D., (by invitation), Birmingham, Ala.
Instructor in Medicine, Medical College of Alabama.

4:00 A Study of Physiologic Mechanisms in Natural Sleep and Hypersomnolent States.

HERBERT O. SIEKER, (Associate), Durham, N. C.
Assistant Professor of Medicine, Duke University School of Medicine; Assistant Chief of Medical Service, Veterans Administration Hospital.

ALBERT HEYMAN, F.A.C.P., Durham, N. C.
Associate Professor of Neurology, Department of Medicine, Duke University School of Medicine; Chief, Neurology Section, Veterans Administration Hospital.

RICHARD I. BIRCHFIELD, M.D., (by invitation), Durham, N. C.
Assistant Resident, Department of Medicine, Duke University School of Medicine, and Veterans Administration Hospital.

4:15 Changes Observed in Human Tracheobronchial Mucosa Due to Uncomplicated Asian Influenza as Revealed by Light and Electron Microscopy.

LAWRENCE F. DIETLEIN, M.D., (by invitation), New Orleans, La.
Senior Assistant Surgeon (R), U. S. Public Health Service, Heart Disease Control Program, Louisiana State Board of Health.

WILLIAM J. MOGABGAB, F.A.C.P., New Orleans, La.
Associate Professor of Medicine, Tulane University School of Medicine.

FRANK N. LOW, Ph.D., (by invitation), New Orleans, La.
Professor of Anatomy, Louisiana State University School of Medicine.

GEORGE E. BURCH, F.A.C.P., New Orleans, La.
Professor and Chairman, Department of Medicine, Tulane University School of Medicine.

4:30 The Use of Inert Foreign Gases in the Diagnosis, Localization and Quantitation of Cardiac Shunts.

EUGENE BRAUNWALD, M.D., (by invitation), Bethesda, Md.
Chief, Section of Cardiology, Clinic of Surgery, National Heart Institute, National Institutes of Health.

ANDREW G. MORROW, M.D., (by invitation), Bethesda, Md.
Chief, Clinic of Surgery, National Heart Institute, National Institutes of Health.

ROBERT T. L. LONG, M.D., (by invitation), Bethesda, Md.
Senior Assistant Surgeon, Clinic of Surgery, National Heart Institute, National Institutes of Health.

4:45 Changes in Heart Rate during Levarterenol Infusion; An Index of Arterial Elasticity.

FRANK A. FINNERTY, JR., M.D., (by invitation), Washington, D. C.
Assistant Professor of Medicine, Georgetown University School of Medicine; Established Investigator, American Heart Association.

JOACHIM H. BUCHHOLZ, M.D., (by invitation), Washington, D. C.
Research Fellow in Medicine, Georgetown University School of Medicine.

GEORGE C. HAJJAR, M.D., (by invitation), Washington, D. C.
Research Fellow in Medicine, Georgetown University School of Medicine.

JOHN TUCKMAN, M.D., (by invitation), Washington, D. C.
Research Fellow in Medicine, Georgetown University School of Medicine.

5:00 ADJOURNMENT.

FOURTH CLINICAL INVESTIGATION SESSION

Waldorf Room, Conrad Hilton Hotel

Thursday, April 23, 1959

Presiding Officer

JACK D. MYERS, F.A.C.P., Pittsburgh, Pa.

SYMPOSIUM ON ECOLOGY OF THE SEALED CHAMBER

Moderator: HARRY J. ALVIS, M.D., (by invitation), Washington, D. C.
Captain, (MC), U. S. Navy; Director, Submarine Medicine Division, Bureau of Medicine and Surgery.

P.M.

2:45 Problems Common to Ships of Inner and Outer Space.
HARRY J. ALVIS, M.D., (by invitation), Washington, D. C.

3:20 Discussion.

3:30 Physiological Stresses Engendered by Acceleration.
CHARLES F. GELL, M.D., (by invitation), Washington, D. C.
Captain, (MC), U. S. Navy; Special Assistant for Medical and Allied Sciences, Office of Naval Research.

4:05 Discussion.

4:15 Surveillance of the Measurement of the Physiological Response to Space Flight.
NORMAN L. BARR, M.D., (by invitation), Washington, D. C.
Captain, (MC), U. S. Navy; Director, Astronautical Medicine Division, Bureau of Medicine and Surgery.

4:50 Discussion.

5:00 ADJOURNMENT.

MORNING LECTURES

These lectures are on Wednesday and Friday mornings. They are planned to present subjects and problems of fundamental importance and timely interest and to enable the speaker to cover his presentation fully with lantern slides and other media of illustration.

They are open to all members and guests of the College by regular registration badge; no special tickets.

Wednesday, April 22, 1959

Grand Ballroom, Conrad Hilton Hotel

Presiding Officer

CHESTER S. KEEFER, F.A.C.P., Boston, Mass.
Regent, A.C.P.

A.M.

9:00 **Stress and Cardiac Infarcts.**
HANS SELYE, M.D., (by invitation), Montreal, Que.
Professor and Director of the Institute of Experimental Medicine and Surgery, University of Montreal Faculty of Medicine.

9:40 **Angina Pectoris.**
MYRON PRINZMETAL, M.D., (by invitation), Los Angeles, Calif.
Clinical Professor of Medicine, University of California School of Medicine at Los Angeles.

10:20 **Diagnostic Applications of the Electroencephalogram.**
REGINALD G. BICKFORD, M.D., (by invitation), Rochester, Minn.
Consultant in Electroencephalography, Mayo Clinic; Professor of Physiology, University of Minnesota (Mayo Foundation).

10:45 **Current Biochemical Concepts of Schizophrenia.**
SEYMOUR S. KETY, M.D., (by invitation), Bethesda, Md.
Chief, Laboratory of Clinical Science, National Institute of Mental Health.

11:15 **ADJOURNMENT.**

Friday, April 24, 1959

Grand Ballroom, Conrad Hilton Hotel

Presiding Officer

THOMAS D. MASTERS, F.A.C.P., Springfield, Ill.

Governor, A.C.P.

A.M.

9:00 **Drugs and Psychotherapy in Medical Practice.**
JULES H. MASSERMAN, M.D., (by invitation), Chicago, Ill.
Professor of Neurology and Psychiatry, Northwestern University Medical School.

9:30 **The Status of Tranquilizing Drugs—1959.**
BENJAMIN BOSHES, M.D., Ph.D., (by invitation), Chicago, Ill.
Professor and Chairman, Department of Neurology and Psychiatry, Northwestern University Medical School.

10:00 **Pulmonary Function Tests.**
WARD S. FOWLER, M.D., (by invitation), Rochester, Minn.
Section of Medicine, Mayo Clinic and Mayo Foundation.

10:30 **Minimization of "Tracer" Doses of Radioisotopes Used in Diagnosis.**
WILLIAM G. MYERS, F.A.C.P., Columbus, Ohio.
Research Professor of Medical Biophysics, Department of Medicine, The Health Center, Ohio State University College of Medicine.

11:10 **ADJOURNMENT.**

CLINICAL-BASIC SCIENCE CASE CONFERENCES

Grand Ballroom, Conrad Hilton Hotel

	Tuesday, April 21	Wednesday, April 22	Thursday, April 23	Friday, April 24
11:30 A.M. to 12:45 P.M.	**Clinical-Basic Science Case Conference** **RENAL CASE** **Moderator** *John P. Merrill Boston **Discussers** *Maurice B. Strauss Boston *Louis G. Welt Chapel Hill **Pathologist** Benjamin H. Spargo Chicago	**Clinical-Basic Science Case Conference** **LIVER, METABOLIC PROBLEM** **Moderator** *Wesley W. Spink Minneapolis **Discussers** *Thomas M. Durant Philadelphia *Leon Schiff Cincinnati **Pathologist** *Edwin F. Hirsch Chicago	**Clinical-Basic Science Case Conference** **PULMONARY PROBLEM** **Moderator** *Richard V. Ebert Little Rock **Discussers** *Alvan L. Barach New York *Roger S. Mitchell, Jr. Denver **Pathologist** Francis J. Tenczar Chicago **Roentgenologist** Earl E. Barth Chicago	**Clinical-Basic Science Case Conference** **CARDIAC PROBLEM #1** **Moderator** *Wright Adams Chicago **Discussers** Howard B. Burchell Rochester *William Dock Brooklyn **Pathologist** Paul B. Szanto Chicago **Roentgenologist** William T. Meszaros Chicago **CARDIAC PROBLEM #2** **Moderator** *Wright Adams Chicago **Discussers** Howard B. Burchell Rochester *William Dock Brooklyn **Pathologist** *Edwin F. Hirsch Chicago **Roentgenologist** William T. Meszaros Chicago

*F.A.C.P.

CLINICAL–BASIC SCIENCE CASE CONFERENCES

These conferences will be held daily, Tuesday through Friday, 11:30 A.M. to 12:45 P.M., in the Grand Ballroom of the Conrad Hilton Hotel. All participants have gained recognition for their contributions in the specific field of medicine under discussion.

All protocols and case reports are provided in the program. For maximum enjoyment and academic harvest from these exercises, we urge you to review this material in advance of the actual session. What are your diagnoses?

Admission will be by badge; no tickets required.

CLINICAL–BASIC SCIENCE CASE CONFERENCE

Grand Ballroom, Conrad Hilton Hotel

Case 1

Tuesday, April 21

11:30 A.M.–12:45 P.M.

RENAL CASE

Moderator: **JOHN P. MERRILL, F.A.C.P., Boston, Mass.**
Assistant Professor of Medicine, Harvard Medical School; Attending Physician, Peter Bent Brigham Hospital.

Discussers: **MAURICE B. STRAUSS, F.A.C.P., Boston, Mass.**
Professor of Clinical Medicine, Boston University School of Medicine.

LOUIS G. WELT, F.A.C.P., Chapel Hill, N. C.
Professor of Medicine, University of North Carolina School of Medicine.

Pathologist: **BENJAMIN H. SPARGO, M.D., (by invitation), Chicago, Ill.**
Assistant Professor in Pathology, The University of Chicago, The School of Medicine.

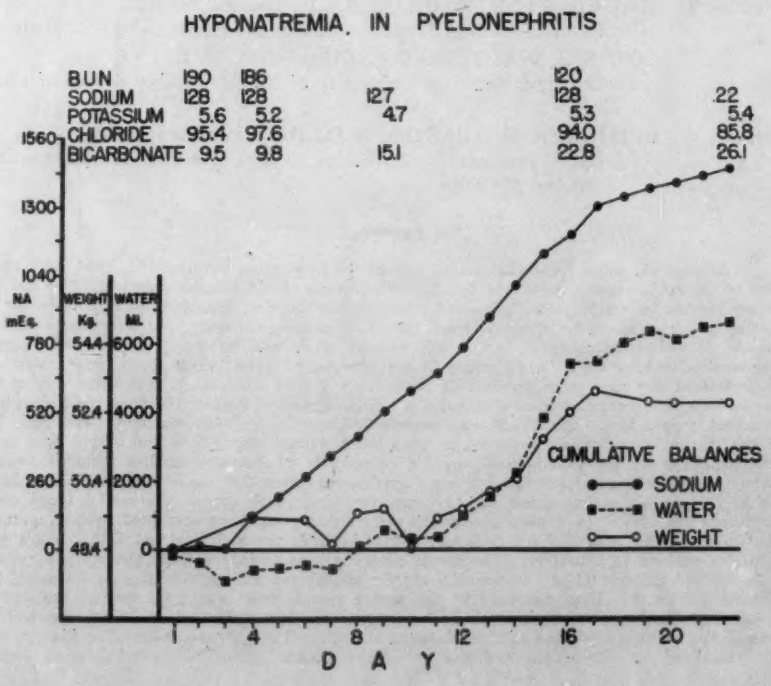
Protocol

A 57-year old white female housewife entered the hospital on February 13, 1954, with symptoms of anorexia, nausea, weakness and light-headedness of six months duration. She had lost twenty pounds in weight. She had noted cloudy urine, urgency, frequency and nocturia for six months and complained of frequent epistaxis. Four years previously, she had experienced an episode of sudden severe pain in the left anterior chest and left upper abdominal quadrant, diagnosed elsewhere as a "heart attack." An electrocardiogram, chest x-ray and intravenous pyelogram at that time were reported as normal. A 2 plus albuminuria was noted during that illness. Physical examination now revealed a well-developed, chronically ill female, with evidence of recent weight loss. The blood pressure was 186 systolic and 104 diastolic. The right lobe of the thyroid was diffusely enlarged to four times normal size. A fibroid uterus was noted. The remainder of the examination was not remarkable. Laboratory studies included negative Kahn; leukocyte count 5,350 per cu. mm.; erythrocyte count 2.94 million per cu. mm.; hemoglobin 7.0 gm.%; sedimentation rate 24 mm. per hour; and normal differential blood count. Urinalysis revealed 1 to 2 plus albuminuria; the urinary sediment contained hyaline, granular and cellular casts, with 3–5 red cells and 3–5 white cells per high powered field. Stools were 0 to 2+ positive to benzidine. The serum electrolytes measured: sodium 138 mEq./L.; potassium 5.2 and chloride 111.2; calcium 7.5 mg.%; phosphorus 5.7 mg.%; albumin 3.6 gm.% and globulin 3.0 gm.%. Urea clearance by the square root formula was 4 ml. per minute and the blood urea nitrogen was 110 mg.%. PSP excretion was less than 10% in 15 minutes and less than 25% in 2 hours. Urine cultures demonstrated *E. coli* and *P. mirabilis*. The kidneys were not visualized by intravenous pyelography. A retrograde pyelogram revealed small kidneys

bilaterally. A chest x-ray, cholecystogram and proctoscopic examination were normal. An electrocardiogram revealed left bundle branch block. The blood pressure averaged 130 systolic and 80 diastolic during the hospital period. The patient was placed on a high fluid intake and received one blood transfusion. The hemoglobin level rose to 13.0 gm.% and the blood urea nitrogen fell to 98 mg.%. She was discharged symptomatically improved on March 22, 1954.

The patient was well until May 1954 (two months later), when she developed ankle swelling, orthopnea and paroxysmal nocturnal dyspnea. The hemoglobin had decreased to 8.4 gm.%; the blood urea nitrogen was 105 mg.%. She was placed on a 1200 mg. sodium diet; dietary protein was restricted to 50 grams per day and she was digitalized. Symptoms improved but digitalis was discontinued one month later because of anorexia and nausea. The dyspnea and ankle swelling subsequently recurred and the patient was hospitalized for the second time on January 7, 1955. On physical examination, the blood pressure was 150 systolic and 96 diastolic. The pulse rate was 136 and regular. The PMI was 3 cm. to the left of the mid-clavicular line in the fifth intercostal space; P_2 was greater than A_2. There was a soft apical systolic murmur which was not transmitted; an apical systolic gallop was present. Fine crepitant rales were heard in both lung bases, posteriorly. Laboratory studies included a leukocyte count of 5400 per cu. mm.; erythrocyte count 2.3 million per cu. mm.; hemoglobin 8.4 gm.% and normal differential blood count. Urinalysis revealed 2+ albuminuria, with hyaline, granular and cellular casts in the centrifuged sediment; there were 10 RBC and 2 WBC per high powered field. The serum electrolytes were: sodium 142 mEq./L.; potassium 5.3 mEq./L.; chloride 109 mEq./L., and CO_2 17 mEq./L.; calcium 8.1 mg.%; phosphorus, 6.4. The serum albumin was 3.9 and globulin 2.8 gm.%; blood urea nitrogen 114 mg.% and blood sugar 100 mg.%. Urine culture was negative. Chest x-ray revealed slight cardiomegaly. The electrocardiogram indicated nonspecific ST segment and T wave changes. The patient was placed on bedrest, a 1200 mg. sodium and 30 gram protein diet and she was digitalized. The pulse rate fell to 80 per minute and she lost 2.5 kg. body weight. Four units of washed red cells were given and the hemoglobin rose to 12.6 gm.%. There was subjective improvement, with disappearance of dyspnea and the gallop rhythm. She was discharged on the low sodium diet and a maintenance dose of digitalis on January 18, 1955.

Two weeks prior to her third admission on April 12, 1955, the patient developed pyuria and dysuria, treated with gantrisin and penicillin. Symptoms improved, but on March 30, 1955,



the hemoglobin was 8.9 gm.%. Physical examination indicated no new findings. Laboratory studies included a leukocyte count of 8,050 per cu. mm.; erythrocyte count 2.5 million per cu. mm.; and hemoglobin 8.5 gm.%. Urinalysis indicated a specific gravity of 1.013 and 2+ albumin. The centrifuged sediment contained 20–25 RBC and 7–10 WBC, with occasional cellular and granular casts. Serum electrolytes (Na, K and Cl) were normal. Serum calcium 7.4 mg.%; serum phosphorus 6.1 mg.%. Albumin 3.9 gm.%; globulin 3.2 gm.%. Urine culture demonstrated *Strep. fecalis*. Chest x-ray revealed cardiomegaly of 18%. A course of tetracycline therapy was instituted and four units of packed red cells were given. The hemoglobin rose to 10.3 gm.%. She was discharged on the previous regime and aluminum hydroxide, 30 ml. four times daily, April 23, 1955.

Three subsequent hospital admissions were for blood transfusions. No new findings were demonstrated. Following discharge from the hospital on September 15, 1955 (sixth hospitalization), the patient developed nausea, vomiting, weakness, malaise, inability to stand, blurred vision and postural light-headedness. Moving from a supine to sitting or standing position produced extreme weakness, blurred vision and nausea with vomiting. These symptoms were relieved by lying down and were so severe she was unable to walk. She was admitted for the seventh time on September 26, 1955, remaining until October 19, 1955. Physical examination indicated a blood pressure of 150 systolic and 70 diastolic in the supine position; and 60 systolic and 40 diastolic in the erect position. The skin and mucous membranes were dry and skin turgor was poor. There were no other findings and there was no evidence for congestive heart failure. Laboratory studies included a leukocyte count of 7,200 per cu. mm.; hemoglobin 10.6 gm.%; erythrocyte count 3.4 million per cu. mm. Urinalysis revealed 2+ albuminuria, with an occasional RBC and WBC in the sediment. Serum electrolytes were: sodium 126 mEq./L.; potassium 5.6; chloride 95.4 and CO_2 10.2 mEq./L.; calcium 5.6 mg.%; phosphorus 4.1 and blood urea nitrogen 190 mg.%.

On the fourth hospital day, sodium was prescribed as both bicarbonate and chloride salts, in doses as high as 12 grams of NaCl and 3.6 grams of $NaHCO_3$ per day. Five days later postural hypotension disappeared, nausea improved, vomiting ceased and the appetite returned. Skin turgor improved and mucosal dryness disappeared. Metabolic balance data are presented in the above graph. During the first nine days of therapy the patient retained 760 milliequivalents of sodium without weight gain. Hyponatremia persisted despite retention of sodium without water. However, the blood urea nitrogen diminished to 120 mg.% and the CO_2 rose to 24 mEq./L. During the next ten days she retained an additional 680 mEq./L. of sodium, with a concomitant weight gain of 4.5 kg. Towards the end of the study, pedal edema developed. The patient was discharged from the hospital much improved and she was instructed to remain on digitalis, sodium bicarbonate, calcium carbonate, and a 3 gram salt, low protein, diet.

Eight days after the previous hospital admission, on October 27, 1955, the patient was readmitted for the eighth and last time, with complaints of ankle swelling, shortness of breath, paroxysmal nocturnal dyspnea, vomiting and a sharp, knife-like pain in the left supraclavicular area. Physical examination revealed a blood pressure of 150/125; the pulse rate was 124 and regular. The patient was acutely ill; the skin was moist and sallow. There were fine crepitant rales in both lung bases, posteriorly. An apical systolic gallop was present and a bi-phasic friction rub was heard over the entire precordium. The liver was palpable 3 cm. below the right costal margin and was not tender. There was 4 plus pitting edema to the mid-calf region. Laboratory studies indicated a leukocyte count of 11,600 per cu. mm.; erythrocyte count 2.2 million per cu. mm.; hemoglobin 6.8 gm.%. The differential blood count revealed 94% polys, 2% lymphocytes, and 4% monocytes. The urine contained 2 plus albumin; the centrifuged urinary sediment contained hyaline, granular and cellular casts, broad "renal failure casts," 1–3 red cells, 10–15 white cells and bacteria. The serum electrolytes were sodium 124 mEq./L.; potassium 4.8; chloride 86.8 mEq./L.; and CO_2 21.8 mEq./L. The serum albumin was 2.4 and the globulin 2.4 gm.%; the blood urea nitrogen was 120 mgm.%.

The patient was treated with a 25 gram protein, 400 mgm. sodium, full liquid diet and with a continuous intravenous drip containing aminophyllin. In addition, she received prednisone, 30 mgm. per day, thorazine, digitalis, and multiple packed red cell transfusions. The friction rub persisted for almost a week. Despite these therapeutic measures the course was steadily downhill. The urinary output decreased, so that on the 6th hospital day, the 24-hour urine totalled only 200 cc. Concurrently, the oliguria and hyponatremia became more severe, and on the 6th hospital day, the serum sodium was 111 mEq./L., serum potassium 5.7, chloride 76.6 mEq./L. and CO_2 17.7 mEq./L. The blood urea nitrogen at this time was 106 mgm.%. Because the prognosis was so poor and, because therapy up to this point had been unsuccessful, triiodothyronine, 100 mgm. was administered in the hope that excretion of water might be increased. Within 48 hours the urinary output increased from 100 cc. per day to 900 cc. per day. At the same time the serum sodium rose from 111 to 124 mEq./L. The blood urea nitrogen rose to 220 mgm.%. The course continued to deteriorate and the patient died quietly on the 14th hospital day (November 10, 1955).

CLINICAL–BASIC SCIENCE CASE CONFERENCE

Grand Ballroom, Conrad Hilton Hotel

Case 2

Wednesday, April 22

11:30 A.M.–12:45 P.M.

LIVER, METABOLIC PROBLEM

Moderator: **WESLEY W. SPINK, F.A.C.P., Minneapolis, Minn.**
Professor of Medicine, University of Minnesota Medical School.

Discussers: **THOMAS M. DURANT, F.A.C.P., Philadelphia, Pa.**
Professor of Medicine, Temple University School of Medicine.

LEON SCHIFF, F.A.C.P., Cincinnati, Ohio.
Professor of Clinical Medicine and Director of Gastric Research Laboratory, University of Cincinnati College of Medicine.

Pathologist: **EDWIN F. HIRSCH, F.A.C.P., Chicago, Ill.**
Associate Professor of Pathology, Emeritus, The University of Chicago, The School of Medicine; Director of Pathology, Henry Baird Favill Laboratory, St. Luke's Hospital.

Protocol

A 42-year old white female, who had been jaundiced for four years, was admitted to the hospital on July 23, 1957, with a fever of 39.2° C., rectally, associated with chills of 24 hours duration. She had had no pain, no symptoms of an upper respiratory infection and no diarrhea or constipation. One day before the onset of fever, she had observed "milk colored" stools. The urine always was orange-colored and was unchanged. Three weeks before admission, she was treated for pleurisy in the right chest, and while in the emergency room on this admission, she had experienced a severe episode of dyspnea. The patient's first admission was in 1944 for observation of a pulmonary problem. She had had a persistent cough without hemoptysis for a year. Other symptoms included weakness, fatigue, and occasional shortness of breath. In September and October of 1945 she was in a sanatorium and examined repeatedly for tuberculosis, with negative findings. Chest x-rays reportedly were suggestive of pneumoconiosis. The PPD No. 2 was strongly positive. Guinea pig inoculations of gastric washings were negative. X-rays demonstrated a diffuse infiltrative process extending from the hilum to the upper lobes. Six years later, in 1950, she again was admitted for a persistent, slightly productive cough. PPD No. 2, histoplasmin, and coccidioidin tests now were negative. Bronchoscopic examination also was negative. The clinical diagnosis was pulmonary fibrosis of unknown etiology. In 1953 she complained of pains in both legs for three years. X-rays of the long bones were negative. Bone marrow aspiration did not reveal significant abnormality. The non-protein nitrogen was 56.5 mg.%. Also, at approximately this time, she noticed intermittent swelling of the abdomen, associated with intermittent jaundice. In November 1955 an enlarged, nodular liver and the spleen were palpable. These findings were confirmed at peritoneoscopy. Liver biopsy at the time of peritoneoscopy was interpreted as demonstrating inflammation. During this hospitalization the patient had an episode of severe hematemesis, requiring 17 blood transfusions. Esophageal varices were demonstrated radiologically on the next admission in January, 1956; gastro-intestinal x-rays otherwise were negative. The alkaline phosphatase at this time was 73.0 units (Bodansky). The total protein was 6.7 gm.%, albumin 2.70 gm.% and globulin 4.0 gm.%. The total bilirubin was 2.4 mg. and the direct, 1.5 mg.%. The thymol turbidity was 7.1 units.

The temperature was 39.2° C. (rectally), the pulse was 80 per minute and the blood pressure 110/70; the respirations were 22 per minute. The patient was severely icteric, with multiple spider nevi and xanthomas of the chest, back and arms, and superficial venous distention of the chest. Other findings were icteric sclerae, coloboma of the right eye, and xanthomas on the eyelids. Dullness to percussion was noted at the level of the fourth rib anteriorly, on the right. The breath sounds were diminished below the fourth rib on the right. There was a low-pitched transitory rubbing sound in the left axilla, more pronounced on inspiration. The chest wall was tender to percussion bilaterally. Cardiac examination demonstrated a rough pulmonic murmur radiating to the neck and over the entire precordium. The abdomen was distended, and tym-

panitic; there was slight tenderness in the right upper quadrant. The liver was palpable eight fingerbreadths below the costal margin, at the level of the anterior axillary line.

The urine was amber in color and cloudy; the pH was 4.5; there was no sugar or albumin; there were many bacteria and uric acid crystals. Other laboratory data included negative Kahn test, hematocrit 37%; white blood cells 7250 per cu. mm.; hemoglobin 12.5 gm.%. The serum cholesterol was 610 mg.%. The total bilirubin was 9.7 and the direct, 6.2 mg.%.

Following admission, the patient was dyspneic and coughing. Crepitant rales were audible in both bases. The temperature ranged between 38° C. and 40° C. The blood pressure was 90/50 and decreased to 76/40. She was treated with morphine sulfate, oxygen tent, and sedation. A few days later she coughed up a blood clot and dyspnea increased. The patient became increasingly icteric and semicomatose. Treatment included achromycin, 500 mg. intravenously, 500 cc. of whole blood, dextrose in water 1000 cc., 500 cc. of NaCl with hydrocortisone, 50 mg., and Vitamin K. The lungs continued to contain crepitant rales in the bases. The temperature was 39.2° C. The blood pressure was maintained with Levophed to 80/40. The respiratory difficulty increased and was not benefited by all therapeutic measures, including Lanatoside "C", 1.2 mg., intravenously. Death occurred on July 29, 1957.

CLINICAL–BASIC SCIENCE CASE CONFERENCE

Grand Ballroom, Conrad Hilton Hotel

Case 3

Thursday, April 23

11:30 A.M.–12:45 P.M.

PULMONARY PROBLEM

Moderator: **RICHARD V. EBERT, F.A.C.P., Little Rock, Ark.**
Professor of Medicine and Head of the Department, University of Arkansas School of Medicine.

Discussers: **ALVAN L. BARACH, F.A.C.P., New York, N. Y.**
Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons.

ROGER S. MITCHELL, JR., F.A.C.P., Denver, Colo.
Associate Professor of Medicine, University of Colorado School of Medicine.

Pathologist: **FRANCIS J. TENCZAR, M.D., (by invitation), Chicago, Ill.**
Assistant Professor of Pathology, Northwestern University Medical School; Associate Pathologist, Chicago Wesley Memorial Hospital.

Roentgenologist: **EARL E. BARTH, M.D., (by invitation), Chicago, Ill.**
Professor and Chairman, Department of Radiology, Northwestern University Medical School; Member of Staff, Passavant Memorial Hospital; Chief Consultant, Radiology, V. A. Research Hospital.

Protocol

A previously healthy 23-year old colored housewife was hospitalized because of cough, shortness of breath and back pain of approximately five months duration. The cough at first was non-productive but soon increased in severity and was productive of two to three tablespoonsful of clear, greenish material daily. The patient frequently experienced feverish sensations and several episodes of associated chills two months before admission. One penicillin injection was administered by her local physician one month before admission. Exertional dyspnea increased progressively and one monh before admission she was forced to markedly limit her household duties and to sleep on several pillows. One week prior to admission, nocturnal dyspnea appeared. At first the back pain was limited to the left scapular region but then appeared elsewhere, particularly in the sacral region. Her appetite was poor and she had lost 38 pounds. Previous hospitalizations included the spontaneous delivery of a normal, full-term infant four years,

and laparotomy for ruptured ectopic pregnancy two years before admission. She had always lived in Chicago, had worked for brief periods at clerical jobs and was of temperate personal habits.

On examination, the patient appeared chronically ill and in definite respiratory distress, with a respiratory rate of 32 per minute. She was unable to lie recumbent because of dyspnea. The temperature was 38.8° C., pulse 110 and regular; the blood pressure was 105/75. The thoracic excursion was symmetrical, with dullness to percussion bilaterally at the lung bases; fine, terminal inspiratory rales were audible in showers at both bases; coarser rales and wheezes were heard at the bases, clearing after coughing. The heart was "over-active" and the apex beat was visible in the fourth intercostal space, 8 cm. to the left of the sternum. A visible pulsation was noted in the second intercostal space, 5 cm. to the left of the sternum. A grade one systolic murmur was audible at the apex. The pulmonic second sound was accentuated, split and considerably louder than the second aortic sound. The remainder of the examination was normal.

Abnormal laboratory tests at this time included: a sedimentation rate (Wintrobe) of 36 mm./hour; sputum culture revealed a heavy growth of hemolytic staphylococcus albus and a moderate growth of non-hemolytic streptococcus; negative tuberculin skin tests. The total proteins were 8.0 grams%, with an albumin of 4.0 grams%. The serum calcium was 9.3 mg.%, inorganic phosphorus 3.5 mg.%, and the alkaline phosphatase 17.3 units (normal 2–4 units). The electrocardiogram demonstrated a slight left axis deviation, flat to inverted T waves in lead I and inverted T waves in leads II, III, VF and in all precordial leads; no ST segment shift was evident; the P-R interval was 0.17 seconds. The rhythm was a sinus tachycardia, at 100 per minute. The chest roentgenogram indicated the transverse cardiac diameter to be 116 mm., representing a 5 to 10% enlargement. There was a prominence of the right ventricle and some exaggeration of the hilar markings. The peripheral lung markings were especially pronounced at the bases and the costophrenic angles were indistinct and blunted. A right apical infiltrate without cavitation was evident.

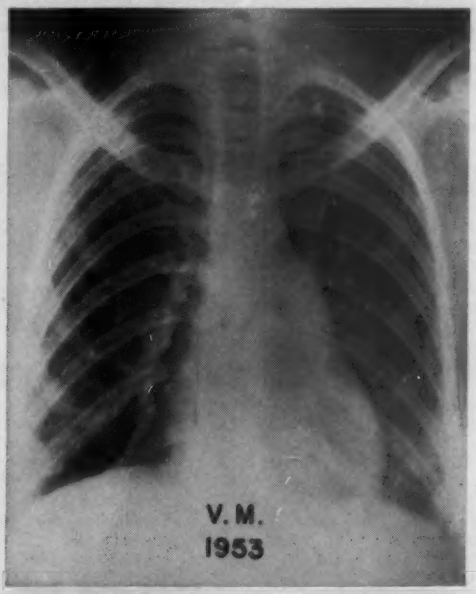
The patient was given nasal oxygen, digitoxin, 600,000 units of crystalline procaine penicillin twice daily and large doses of aspirin. Her condition did not change for two weeks. The temperature varied between 37.2° C. and 38.3° C. daily. The pulmonary findings remained unchanged but a low-pitched, mid-diastolic rumble became audible at the 3rd left intercostal space. The previously noted systolic murmur was transient and not always present, but the mid-diastolic rumble persisted. Additional laboratory findings were: persistently elevated erythrocyte sedimentation rate, serum proteins of 6.9 grams%, equally divided between the albumin and globulin fractions; minor T wave changes compared with the original electrocardiograms but the P-R interval measured 0.20 seconds on two occasions when the heart rate was 88 and 68 per minute. Sinus x-rays demonstrated clouding in the frontal and ethmoid sinuses. The mucous membrane of both maxillary antra was thickened. X-rays of the sella turcica revealed a minimal increase in its antero-posterior diameter, but a smaller than average superior-inferior diameter.

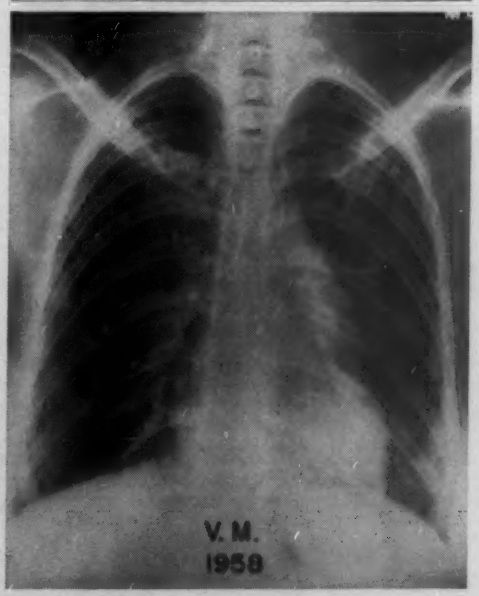
Therapy included hydrocortisone (40 mg. daily) and rigid sodium restriction. Within 48 hours there was a prompt defervescence, and a pronounced decrease in symptoms. Soon thereafter a fecal impaction was removed; the patient subsequently had an alarming amount of rectal bleeding. Proctoscopic examination revealed internal hemorrhoids but no bleeding point to 18 centimeters. A small amount of red blood appeared to originate above the level of the proctoscope. The prothrombin time was 60% after 72 mg. of vitamin K. Salicylates and steroids were discontinued. The fever promptly recurred and pulmonary congestion apparently increased. Two weeks later hydrocortisone (50 mg. per day), penicillin and streptomycin were instituted, but the patient remained febrile, with a temperature to 40° C. daily. After two weeks on hydrocortisone, ACTH (25 units every 12 hours) was substituted with prompt disappearance of fever. Finally, the patient was discharged on hydrocortisone, 60 mg. daily. It was not possible to reduce the hydrocortisone below this level without recurrence of pain and fever. At the time of discharge, the patient had a prominent systolic murmur in the left third intercostal space at the border of the sternum and the second pulmonic sound was extremely loud and snapping. No abdominal organs were palpable and the lungs were clear. The blood pressure was 110/90 mm. Hg. There was moderate hirsutism, slight moon face and acne of the face and chest. The patient felt well.

One month later the patient was hospitalized again because of recurrent pain and fever, their onset coinciding with a reduction of hydrocortisone to 35 mg. daily. The physical findings at this time were the same as noted at the time of discharge one month earlier. The electrocardiogram indicated a P-R interval of 0.20 seconds at a heart rate of 88 per minute; this gradually decreased to 0.16 seconds at a rate of 100 per minute shortly before discharge. The patient was discharged on 30 mg. of hydrocortisone and 0.1 mg. of digitoxin daily.

During the following year the patient was observed in the out-patient department. Every attempt to reduce the steroid dose below 30 mg. per day resulted in malaise, fever and increased sedimentation rate. The digitoxin was discontinued. Two years after the onset of illness, the patient was hospitalized again because of a ruptured ectopic pregnancy. A total abdominal hysterectomy and right salpingo-oophorectomy were performed. A cervical lymph node biopsy was

performed at this time. Large doses of hydrocortisone were administered before, during and after surgery. The patient had a prolonged post-operative course with persistent elevation of temperature but she gradually recovered and left the hospital without medication. After further convalescence at home she returned for additional tests; the results are tabulated on the next page. During the subsequent year, despite persistently negative tuberculin skin tests, bilateral apical pulmonary cavities developed. Two sputum cultures were positive for acid-fast bacilli, but further study revealed that the organisms were avirulent, and subsequent cultures were negative. She continues to feel well despite no therapy.





PULMONARY FUNCTION TESTS

	Observed	*Predicted*	*% Predicted*
(1) *Ventilation Studies*			
Maximal breathing cap., L/min.	99	96	103%
Vital capacity, ml.	1560	3260	48%
Timed vital capacity			
1 sec. % of total	88%	75%	
2 sec. % of total	94%	85%	
3 sec. % of total	96%	90%	
Total lung volume, ml.	2425	4075	60%
Residual lung vol., ml.	1030	815	126%
Residual vol./Tot. vol. ratio	43%	20–25%	
(2) *Arterial Blood Gases*			
Exercise, room air			
CO_2 content, vol. %	36.5	47–55	
Oxygen saturation, %	89.8	97–99	
Rest, breathing room air			
CO_2 content, vol. %	42.3	45–55	
Oxygen saturation, %	92.8	96–98	
(3) *Exercise Metabolism*			
1.5 miles per hour at 5% grade:			
Oxygen consumption, ml./min.	737	—	
Ventilation, L/min.	28.4	—	
Ventilatory equivalent	3.9	2.2–2.5	
Carbon monoxide diffusion capacity, ml./min./mm. Hg	4.1	20–30	

CARDIAC CATHETERIZATION

	Systolic	*Diastolic*	*Mean*
Pressures (mm. Hg)			
Right auricle	1	−3	−1
Right ventricle	18	−2	—
Pulmonary artery	18	5	10
Pulmonary "wedge"	10	2	—
Brachial artery	100	65	98

Cardiac index, L/min., equals 4.2

Oxygen content of blood samples from the heart revealed no evidence of a shunt.

CLINICAL–BASIC SCIENCE CASE CONFERENCE

Grand Ballroom, Conrad Hilton Hotel

Case 4

Friday, April 24

11:30 A.M.–12:30 P.M.

CARDIAC PROBLEM #1

Moderator: **WRIGHT ADAMS, F.A.C.P., Chicago, Ill.**
Professor of Medicine and Chairman of the Department, The University of Chicago, The School of Medicine.

Discussers: **HOWARD B. BURCHELL, M.D., (by invitation), Rochester, Minn.**
Professor of Medicine, University of Minnesota (Mayo Foundation).

WILLIAM DOCK, F.A.C.P., Brooklyn, N. Y.
Professor of Medicine, State University of New York College of Medicine at New York City.

Pathologist: **PAUL B. SZANTO, M.D., (by invitation), Chicago, Ill.**
Professor of Pathology, The Chicago Medical School; Director, Department of Pathology, Cook County Hospital.

Roentgenologist: **WILLIAM T. MESZAROS, M.D., (by invitation), Chicago, Ill.**
Associate Professor of Roentgenology, Cook County Postgraduate School of Medicine; Director, Diagnostic Roentgenology, Cook County Hospital.

Protocol

A 40-year old Negro female first had been admitted to the hospital on December 30, 1953, with a history of cough, shortness of breath and orthopnea occurring predominantly during the previous two or three winters. In February, 1953, she had been hospitalized in another city for similar complaints, and was told her heart was enlarged. The patient could walk about one mile, but became dyspneic on climbing two flights of stairs; there was no history of hypertension or rheumatic fever. She acknowledged treatment for syphilis twenty years previously, and had had numerous miscarriages. She slept on two pillows during the winters, and occasionally would experience paroxysmal nocturnal dyspnea several times during the night. There had been a ten pound weight loss in the previous two months. There was no history of ankle edema, hemoptysis, or chest pain.

On admission in 1953, the blood pressure was 120/100, apical rate regular, 140/min.; temperature 99° F., respirations 30/min. There was 1 + distention of the cervical veins. The fingers and toes were moderately clubbed and the nailbeds were cyanotic. The cardiac apex was palpated in the anterior axillary line, 6th interspace; no thrills were felt. The heart tones were distant over the base; the second sound was louder in the 2nd left intercostal space. The second sound at the apex was split; a rumbling murmur at the apex was described by some observers. The chest was clear. Femoral pulsations were strong bilaterally. The patient received digitalis, a low salt diet, ammonium chloride and penicillin. The circulation time, arm to tongue, was 7 sec. and arm to lung 13 sec. Serology was negative. Four 24 hour sputa were negative for acid fast bacilli and two sputa were reported to contain acid fast rods, not typical of tubercle bacilli. The non-protein nitrogen and total plasma proteins were normal; the serum chloride, sodium, potassium and CO_2 were normal.

Chest x-rays and fluoroscopy revealed the heart increased in its transverse size, with the main pulmonary artery and secondary branches of the right main pulmonary artery abnormally large. The aorta was described as small, and the lung fields were clear. An electrocardiogram demonstrated a definite right axis shift, sinus rhythm, incomplete right bundle branch block, tall and peaked P-waves and an r/S complex to V_6. The results of a cardiac catheterization (1/7/54), ventilatory studies, blood counts and urinalysis are listed at the conclusion of the case report.

Ten months later, November 3, 1954, the patient was admitted with a history of a severe paroxysmal coughing, followed by shortness of breath and then a rapid heart action, increasing the dyspnea. She was acutely dyspneic, with a respiratory rate of 60/min.; the lips and hands were cyanotic. Relief was obtained following digitoxin 0.4 mg. intravenously and meperidine subcutaneously. The non-protein nitrogen was 30 mg.%; one blood culture was negative; the chest x-ray was unchanged.

Two months later, January 6, 1955, the patient was admitted because of cough, shortness of breath and orthopnea. She was markedly dyspneic, orthopneic and cyanotic. The blood pressure was 100/80 and the pulse 108/min. The lungs were clear on auscultation. The first heart sound was described as split. Various blood chemical analyses were normal. Fluoroscopy and x-rays of the chest were unchanged. A plain film of the abdomen was said to demonstrate a large liver. The electrocardiogram was interpreted as indicating right ventricular hypertrophy. Treatment consisted of digitoxin, aminophylline and penicillin. The patient was discharged after eleven days. She was readmitted on two occasions in the following two months with similar complaints. The lungs were clear to auscultation and resonant on percussion. On the second admission one observer described the left heart border 11 cms. from the mid-sternal line. The point of maximum impulse was in the 5th interspace 1 cm. to the left of the midclavicular line. There was an increase in percussion dullness in the 3rd left intercostal space. The second sound was louder over the pulmonary area. A grade II systolic murmur was heard at the apex; in addition, a short diastolic murmur was audible at the apex and in the 4th left intercostal space; this was interpreted by another observer to be a precordial rub. Treatment was as before, with the addition of phlebotomy. On both occasions the patient was discharged within ten days.

Four months later (July 12, 1955) the patient was readmitted for two weeks with similar complaints. The neck veins were distended and a positive hepatojugular reflux was elicited. The first sound was split at the apex and a systolic gallop was heard over this area. Moist rales were audible in the lung bases. The venous pressure was 250 mm. H_2O; ether time was 15 sec. and magnesium sulfate time was 17–18 sec. Chest x-rays were unchanged except for a hazy density in the right mid-lung field. The electrocardiogram was unchanged. The total plasma proteins, cholesterol and non-protein nitrogen were normal.

Two weeks later (August 9, 1955) the patient was readmitted because of nocturnal dyspnea and was discharged four days later. The lungs were clear. The electrocardiogram and chest x-ray were similar to those of previous admissions; no density was noted in the right mid-lung field. Three weeks after the previous hospitalization (September 3, 1955) the patient returned for several weeks because of acute shortness of breath. The physical examination was unchanged. A tuberculin test (dilution 1:1000) was positive. Respiratory function studies performed on this admission are reported at the end of the case report. Treatment again was supplemented by phlebotomy and also by diamox.

On February 8, 1956, the patient was admitted for one week because of shortness of breath. Other than an apical short, presystolic murmur noted by one observer, the findings were unchanged. Non-protein nitrogen, total plasma protein, sodium and potassium levels were normal. The chest x-ray was unchanged. Another admission for six days followed on March 16, 1956, for the same complaints. Six weeks later the patient was readmitted for three weeks because of shortness of breath and a feeling of tightness in the chest. The findings were unchanged. A patchy density was described in the lower right lung field. This was not confirmed by tomography (8/31/56) although the report of this procedure described the pulmonary blood vessels as "quite large" and the left main bronchus as "elevated." The serum electrolytes were normal and the non-protein nitrogen 30 mg.%. The electrocardiogram continued to demonstrate right bundle branch block.

About one month after the previous discharge on October 10, 1956, the patient was readmitted for shortness of breath. She again was markedly cyanotic and dyspneic, with a few audible rales in the lungs. The patient received aminophylline, oxygen, digitalis, phenobarbital, thorazine, and was discharged on October 27, 1956.

The patient was admitted for the last time on November 24, 1956, complaining of severe shortness of breath, a non-productive cough and orthopnea. She had had numerous previous admissions for "asthma." The patient was markedly dyspneic and orthopneic, with visible cyanosis. The blood pressure was 130/80, pulse regular at 100/min.; no heart murmurs were described. The lung fields were clear to auscultation. The liver edge was palpated one finger breadth below the costal margin; a trace of ankle edema was detected. The patient was receiving digitalis; coramine, thorazine, phenobarbital and aminophylline also were given. Twelve hours before death intermittent oxygen by mouth was started with apparent improvement. On November 28 the patient died suddenly while getting out of bed.

Representative Laboratory Data

Peripheral Blood Counts

Date	*Hgb.*	*RBC*	*WBC*
1/6/54	105	—	9,700
11/4/54	109	5.74	13,800
2/12/55	112	5.66	9,650
7/13/55	120	6.60	13,000
2/9/56	99	—	11,500
10/10/56	116	6.56	18,100

Platelets were normal. The differential blood smear usually was normal.

Urinalysis

Date	*S.G.*	*pH*	*Alb.*	*Sugar*	*Micro*
1/3/54	1016	Alk	Tr.	0	Few casts
11/3/54	1015	Alk	1 plus	0	2–6 RBCs/hpf
2/11/55	1010		1 plus	0	20–30 WBCs/hpf
7/12/55	1011		4 plus	0	—
8/23/56	—	Acid	2 plus	0	Loaded with WBCs and few RBCs

HEART LABORATORY

Right Heart Catheterization Data

Height: 59 in.
Weight: 92 lbs.
Surf. Area: 1.3 M^2

Blood Oxygen Content, Vols. %

Rest:

Superior Vena Cava	11.47
Right Atrium—Middle	12.35
Right Atrium—Lower	10.33
Right Ventricle—Middle	12.38
Pulmonary Artery—Main	12.86
Pulmonary Artery—Right	12.67
Left Atrium	18.28 (Satn. 73.2%)
Right Femoral Artery	17.89 (Satn. 71.9%)
Arterial Oxygen Capacity	24.90
Hemoglobin	18.3 grams
Ear Oximetry (1/8/54)	85% rest
(3 min. 100% O_2 mask)	96%

Intravascular Pressure, S/D (mean)

Rest:

	mm. Hg
Right Atrium	(2)
Right Atrium "a" Wave	2
Right Ventricle	61/5 (26)
Pulmonary Artery	65/30 (42)
Pulmonary Capillary	(11)
Left Atrium	(3)
Left Atrium "a" Wave	8
Right Femoral Artery	92/50 (64)

Exercise (Very Mild):

Pulmonary Artery	65/31 (42)
Pulmonary Capillary	(9)

Heart Rate: (Sinus Rhythm): Oxygen Consumption:
Rest—96/min. Rest—218 cc./min.
Exercise—96/min.

Cardiac Outputs:

Rest:

	L/min.	*cc./stroke*	*Index, L/M^2 min.*	*Normal Index*
Systemic	3.40	35.4	2.56	3.0–3.5
Pulmonary	4.26	44.4	3.20	3.0–3.5

Ventilatory Studies (1/8/54)

Tidal Air	750 cc.
Vital Capacity	2400 cc.
Inspiratory Capacity	1675 cc.
Expiratory Reserve Volume	725 cc.
Maximum Breathing Capacity	31.5 L.

Chest Hospital—

Ventilatory Studies (9/29/55)

Oxygen Consumption	439 cc./min.
Vital Capacity	1536 cc.
Resting Minute Volume	17.2 L/min.
Maximum Breathing Capacity	63.3 L/min.

Friday, April 24

12:30 P.M.–12:45 P.M.

CARDIAC PROBLEM #2

Moderator: **WRIGHT ADAMS, F.A.C.P., Chicago, Ill.**
Professor of Medicine and Chairman of the Department, The University of Chicago, The School of Medicine.

Discussers: **HOWARD B. BURCHELL, M.D., (by invitation), Rochester, Minn.**
Professor of Medicine, University of Minnesota (Mayo Foundation).

WILLIAM DOCK, F.A.C.P., Brooklyn, N. Y.
Professor of Medicine, State University of New York College of Medicine at New York City.

Pathologist: **EDWIN F. HIRSCH, F.A.C.P., Chicago, Ill.**
Associate Professor of Pathology, Emeritus, The University of Chicago, The School of Medicine; Director of Pathology, Henry Baird Favill Laboratory, St. Luke's Hospital.

Roentgenologist: **WILLIAM T. MESZAROS, M.D., (by invitation), Chicago, Ill.**
Associate Professor of Roentgenology, Cook County Postgraduate School of Medicine; Director, Diagnostic Roentgenology, Cook County Hospital.

Protocol

A 50-year old white female was admitted on January 8, 1957, with a history of easy fatigability for many years and progressive exertional dyspnea and orthopnea, associated with ankle edema of one year's duration. She was never cyanotic. One month prior to admission, she developed signs of congestive heart failure and was hospitalized elsewhere. Treatment included oxygen, aminophyllin, digitalis, diuretics and bed rest. She improved remarkably and lost twenty pounds of weight in one month. X-rays of the chest at that time indicated cardiomegaly and pulmonary congestion. The electrocardiogram revealed a right bundle branch block, ventricular premature contractions, right ventricular enlargement, sinus tachycardia and an old septal infarct.

Physical examination indicated a well developed, obese female, in no respiratory distress. The blood pressure was 140/80 mm. Hg, pulse 80 but irregular and the respirations 20 per minute. The lungs were clear. Auscultation of the heart revealed a grade III systolic murmur in the third left intercostal space, with many premature ventricular systoles. Examination of the abdomen was negative. There was no edema of the extremities; the peripheral pulses were palpable and strong.

The hemoglobin was 14.7 gms., hematocrit 48%, leukocytes 10,000, with polys 66%, lymphocytes 31%, monocytes 3%. Urinalysis was negative. The sedimentation rate was 80 mm., non-protein nitrogen 34 mg.%, total plasma proteins 6.1 gm.%, albumin 3.2, globulin 2.9. Cardiac fluoroscopy revealed a definitely enlarged heart, increased pulmonary vascularity and a small aortic knob. Phonocardiograms revealed a grade III systolic murmur, with maximum intensity in the second and third left intercostal spaces; the location and type of the murmur suggested that it originated from the pulmonic valve. Cardiac catheterization revealed an atrial septal defect.

With the clinical diagnosis of atrial septal defect, the patient was prepared for cardiac surgery. She was digitalized for four days and on January 23, 1957, the heart was surgically explored under hypothermia. The defect in the intra-atrial septum was too large to be closed under hypothermia and the repair of the defect was postponed. The patient then was prepared for a total cardiac by-pass with the heart-lung machine. She was re-explored on February 5, 1957 and the atrial septal defect was repaired with a polyvinyl sponge graft. Following surgery, the patient's general condition was poor. She remained comatose; respirations were labored, the pulse was weak and rapid and the blood pressure frequently was not recordable. The same evening of the day of cardiac surgery a tracheotomy was performed. The patient's general condition remained very poor and she was kept in the recovery room. She finally died on February 9, 1957.

PANEL DISCUSSIONS

Topics of interest and practical value to all members of the College have been chosen. Qualified men have been selected as Moderators and Panelists. All Panels are scheduled from Tuesday through Friday, from 11:30 A.M. to 12:45 P.M., in the rooms indicated on the preceding charts.

Tickets will be required for certain Panels as indicated in the headings of the chart. Where capacities are limited, admission by ticket will be enforced. Applications for tickets to Panels may be made in advance by MEMBERS on a regular application form which accompanies this program. Tickets will also be available at the Registration Bureau. NON-MEMBERS may not register for Panels by mail, but should secure their tickets directly at the Registration Bureau at the meeting.

Members may submit in writing three weeks before the Session, through the Executive Secretary of the College, questions concerning any phase of the subjects listed. The application form for tickets will also provide space on which to fill in these questions. Moderators and Panelists will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions, including questions from the floor, as time permits.

PANEL DISCUSSIONS

Conrad Hilton Hotel

	Blackstone Theatre (Admission by badge; no tickets)	Eighth Street Theatre (Admission by badge; no tickets)	Williford Room (Admission by badge; no tickets)	Normandie Lounge (Admission by ticket only)	Waldorf Room (Admission by ticket only)	Boulevard Room (Admission by ticket only)
Capacity	2500	1300	900	600	450‡	450§
Tuesday April 21 11:30 A.M. to 12:45 P.M.	**P-1** **The Physiologic Bases for Diagnostic Methods in Liver Disease** Moderator *Hyman J. Zimmerman Chicago *Richard B. Capps Chicago *Frederick W. Hoffbauer Minneapolis *Leslie Zieve Minneapolis	**P-2** **Urinary Tract Infection** Moderator Edward H. Kass Boston Abraham I. Braude Pittsburgh †George Gee Jackson Chicago *Ellard M. Yow Houston	**P-3** **Absorption and Malabsorption** Moderator *Joseph B. Kirsner Chicago *Franz J. Ingelfinger Boston Henry D. Janowitz New York †Harold H. Scudamore Rochester	**P-4** **Serotonin Interrelations** Moderator Albert Sjoerdsma, Jr. Bethesda *Arthur C. Corcoran Cleveland *Harold E. Himwich Galesburg Sidney Udenfriend Bethesda Jan Waldenstrom Malmo, Sweden	**P-5** **For What Are We Training Medical Residents?** Moderator *Wm. B. Bean Iowa City *Ward Darley Evanston *John C. Leonard Hartford †Armand Littman Chicago	**P-6** **Problems of Hypometabolism** Moderator *James H. Means Boston Milton W. Hamolsky Boston *F. Raymond Keating, Jr. Rochester *Theodore B. Schwartz Chicago
Wednesday April 22 11:30 A.M. to 12:45 P.M.	**P-7** **Arteriosclerosis** Moderator *William Dock Brooklyn *Laurance W. Kinsell Oakland Jeremiah Stamler Chicago Fredrick J. Stare Boston *Charles F. Wilkinson, Jr. New York	**P-8** **Electrocardiography—Problem Electrocardiograms** Moderator *George E. Burch New Orleans *Joseph M. Barker Beverly Hills *John S. Graettinger Chicago *Franklin D. Johnston Ann Arbor	**P-9** **The Serology of Collagen and Rheumatic Diseases** Moderator *Joseph J. Bunim Bethesda *William D. Robinson Ann Arbor Lawrence E. Shulman Baltimore †Gene H. Stollerman Chicago	**P-10** **Plain Roentgen Film of the Abdomen: Uses and Pitfalls** Moderator Paul C. Hodges Chicago William R. Eyler Detroit Richard K. Gilchrist Chicago Roscoe E. Miller Indianapolis *Walter L. Palmer Chicago	**P-11** **Myocardopathy—What, How, and Why?** Moderator *Clarence de la Chapelle New York Albert I. Rubenstone Chicago †Louis A. Selverstone Boston *George C. Sutton Evanston	**P-12** **Impact of Population Increase on Medicine** Moderator *John B. Youmans Washington Talcott Parsons Cambridge John Rock Brookline *Walter S. Wiggins Chicago

* F.A.C.P.
† Associate.

‡ Astoria Room and Dining Room #3 are overflow rooms equipped with loudspeakers.
§ Beverly Room, third floor, is overflow room equipped with loudspeakers.

PANEL DISCUSSIONS

Conrad Hilton Hotel

	Blackstone Theatre (Admission by badge; no tickets)	Eighth Street Theatre (Admission by badge; no tickets)	Williford Room (Admission by badge; no tickets)	Normandie Lounge (Admission by ticket only)	Waldorf Room (Admission by ticket only)	Boulevard Room (Admission by ticket only)
Capacity	2500	1300	900	600	450‡	450§
Thursday April 23 11:30 A.M. to 12:45 P.M.	**P-13** **Follow-up after Cardiac Surgery** Moderator †James A. Campbell Chicago; Harper K. Hellems Detroit; Ormand C. Julian Chicago; Willis J. Potts Chicago	**P-14** **The Legitimate Uses of Adrenocortical Steroids** Moderator *Philip S. Hench Rochester; *Samuel M. Feinberg Chicago; Joseph W. Jailer New York; *Mark H. Lepper Chicago	**P-15** **Renal Tubular Function and Dysfunction** Moderator Robert W. Berliner Bethesda; Theodore N. Pullman Chicago; †William B. Schwartz, Jr. Boston; *Louis G. Welt Chapel Hill	**P-16** **The Adolescent and the Internist** Moderator T. William Lester Hinsdale; Robert D. Heas Chicago; Robert P. Masland, Jr. Boston; Clifton C. Rhead, Jr. Chicago	**P-17** **The Treatment of Hemorrhagic Diseases** Moderator *Eugene L. Lozner Syracuse; *William Dameshek Boston; *William J. Harrington St. Louis; Mario Stefanini Boston	**P-18** **Diseases of Muscle Metabolism** Moderator Derek E. Denny-Brown Boston; John S. Garvin Chicago; Laszlo Lorand Evanston; Jack Metcoff Chicago
Friday April 24 11:30 A.M. to 12:45 P.M.		**P-19** **Progress Report on Hypertension** Moderator *Edgar V. Allen Rochester; *Edward D. Freis Washington; †John H. Moyer, III Philadelphia; *Irvine H. Page Cleveland	**P-20** **Questions and Answers in Diabetes** Moderator *Alexander Marble Boston; *Garfield G. Duncan Philadelphia; †Harvey C. Knowles Cincinnati; Rachmiel Levine Chicago; *Randall G. Sprague Rochester	**P-21** **The Needle Biopsy—When and Why?** Moderator *Hugh H. Hussey, Jr. Washington; Matthew H. Block Denver; *Sol Katz Washington; Robert C. Muehrcke Chicago	**P-22** **Infections That are Hard to Treat** Moderator *Lowell A. Rantz San Francisco; †Edwin D. Kilbourne New York; *Vernon Knight Nashville; *Ralph R. Tompsett Dallas	**P-23** **Is There a Future to the Chemotherapy of Cancer?** Moderator David A. Karnofsky New York; Warren H. Cole Chicago; *Samuel G. Taylor, III Chicago; Charles G. Zubrod Bethesda

* F.A.C.P.
† Associate.

‡ Astoria Room and Dining Room #3 are overflow rooms equipped with loudspeakers.
§ Beverly Room, third floor, is overflow room equipped with loudspeakers.

PANEL DISCUSSIONS

Tuesday, April 21

11:30 A.M.–12:45 P.M.

Panel P–1

Blackstone Theatre

The Physiologic Bases for the Diagnostic Methods in Liver Disease.

Moderator: HYMAN J. ZIMMERMAN, F.A.C.P., Chicago, Ill.
Professor and Chairman, Department of Medicine, The Chicago Medical School.

RICHARD B. CAPPS, F.A.C.P., Chicago, Ill.
Clinical Associate Professor of Medicine, University of Illinois College of Medicine.

FREDERICK W. HOFFBAUER, F.A.C.P., Minneapolis, Minn.
Professor of Medicine, University of Minnesota Medical School.

LESLIE ZIEVE, F.A.C.P., Minneapolis, Minn.
Associate Professor of Medicine, University of Minnesota Medical School; Director, Radioisotope Unit (Research), Veterans Administration Hospital.

The basis for diagnostic measures which may be applied in patients with jaundice, hepatomegaly, ascites or gastrointestinal bleeding will be discussed. Application of hepatic function tests to the diagnosis of non-hepatic disease will also be considered.

Tuesday, April 21

11:30 A.M.–12:45 P.M.

PANEL P–2

Eighth Street Theatre

Urinary Tract Infection.

Moderator: EDWARD H. KASS, M.D., (by invitation), Boston, Mass.
Associate Professor of Bacteriology and Immunology, Harvard Medical School.

ABRAHAM I. BRAUDE, M.D., (by invitation), Pittsburgh, Pa.
Professor of Medicine, University of Pittsburgh School of Medicine.

GEORGE GEE JACKSON, (Associate), Chicago, Ill.
Associate Professor of Medicine and Preventive Medicine, University of Illinois College of Medicine.

ELLARD M. YOW, F.A.C.P., Houston, Tex.
Professor of Medicine, Baylor University College of Medicine.

This discussion will include:

Pathogenesis—The influence of obstructive uropathy, renal injury and other predisposing factors;

Ecology—The bacteriological problems, including the contribution of renal biopsy;

Natural History—The significance of asymptomatic bacteriuria and the problems of hypertension, toxemia, diabetes, and course of the disease;

Therapy—The role of instrumentation and surgery, antibacterial agents, etc.

Tuesday, April 21

11:30 A.M.–12:45 P.M.

PANEL P–3

Williford Room

Absorption and Malabsorption.

Moderator: JOSEPH B. KIRSNER, F.A.C.P., Chicago, Ill.
Professor of Medicine, The University of Chicago, The School of Medicine.

FRANZ J. INGELFINGER, F.A.C.P., Boston, Mass.
Professor of Medicine, Boston University School of Medicine.

HENRY D. JANOWITZ, M.D., (by invitation), New York, N. Y.
Department of Medicine, Mount Sinai Hospital.

HAROLD H. SCUDAMORE, (Associate), Rochester, Minn.
Instructor in Medicine, University of Minnesota (Mayo Foundation).

Dynamics of absorption in the normal bowel and the biochemical activity of the tissue related to this will be described. The types of malabsorption syndrome and the methods of diagnosis will be outlined. The pathophysiology of malabsorption and treatment based on physiologic principles will be discussed.

Tuesday, April 21

11:30 A.M.–12:45 P.M.

PANEL P–4

Normandie Lounge

Serotonin Interrelations.

Moderator: ALBERT SJOERDSMA, JR., M.D., (by invitation), Bethesda, Md.
Chief, Section of Experimental Therapeutics, National Heart Institute, National Institutes of Health.

ARTHUR C. CORCORAN, F.A.C.P., Cleveland, Ohio.
Assistant Director, Research Division, Cleveland Clinic.

HAROLD E. HIMWICH, F.A.C.P., Galesburg, Ill.
Director, Research Division, Galesburg State Research Hospital.

SIDNEY UDENFRIEND, Ph.D., (by invitation), Bethesda, Md.
Chief, Laboratory of Clinical Biochemistry, National Heart Institute, National Institutes of Health.

JAN WALDENSTROM, M.D., (by invitation), Malmo, Sweden.
Professor of Clinical Medicine, University of Lund.

There has been a rapid advance in knowledge concerning the physiologic roles of serotonin (5-hydroxytryptamine) under normal and pathologic conditions. The significant scientific developments in this growing field will be reviewed and an attempt made to place clinical applications in proper perspective. Medical problems to be discussed from this standpoint include: mental disease, allergy, hemostasis, hypertension, the carcinoid syndrome, gastrointestinal diseases, and responses to drugs such as reserpine and iproniazid.

Tuesday, April 21

11:30 A.M.–12:45 P.M.

PANEL P–5

Waldorf Room

For What are We Training Medical Residents?

Moderator: WILLIAM B. BEAN, F.A.C.P., Iowa City, Iowa.
Professor of Medicine and Head of the Department of Internal Medicine, State University of Iowa College of Medicine.

WARD DARLEY, F.A.C.P., Evanston, Ill.
Executive Director, Association of American Medical Colleges.

JOHN C. LEONARD, F.A.C.P., Hartford, Conn.
Clinical Director and Director of Medical Education, Hartford Hospital.

ARMAND LITTMAN, (Associate), Chicago, Ill.
Clinical Assistant Professor of Medicine, University of Illinois College of Medicine.

Questions for consideration include the roles of certifying boards, sub-specialties, and graduate degrees in various training programs; also the role of the internist as a practitioner and possibly his roles in research and medical teaching; also a comparison of the roles of internist and general practitioner as the future "family doctor."

Tuesday, April 21

11:30 A.M.–12:45 P.M.

Panel P–6

Boulevard Room

Problems of Hypometabolism.

Moderator: JAMES HOWARD MEANS, F.A.C.P., Boston, Mass.
Jackson Professor of Clinical Medicine, Emeritus, Harvard Medical School; Honorary Physician, Massachusetts General Hospital.

MILTON W. HAMOLSKY, M.D., (by invitation), Boston, Mass.
Assistant Professor of Medicine, Harvard Medical School; Associate in Medical Research, Beth Israel Hospital.

F. RAYMOND KEATING, JR., F.A.C.P., Rochester, Minn.
Professor of Medicine, University of Minnesota (Mayo Foundation); Head of a Section in Medicine, Mayo Clinic.

THEODORE B. SCHWARTZ, F.A.C.P., Chicago, Ill.
Associate Professor of Medicine, University of Illinois College of Medicine; Director, Division of Endocrinology and Metabolism, Presbyterian-St. Luke's Hospital.

Hypometabolism occurs in the absence of intrinsic diseases of the thyroid, as in hypopituitarism, hypoadrenalism, hypogonadism, induced hypothermia, certain psychoses, etc. The discussion will concern itself with these problems as well as a discussion of "non-thyroidal hypometabolism" (the metabolic insufficiency syndrome).

Wednesday, April 22

11:30 A.M.–12:45 P.M.

PANEL P–7

Blackstone Theatre

Arteriosclerosis.

Moderator: WILLIAM DOCK, F.A.C.P., Brooklyn, N. Y.
Professor of Medicine, State University of New York College of Medicine at New York City.

LAURANCE W. KINSELL, F.A.C.P., Oakland, Calif.
Director, Institute for Metabolic Research, Highland-Alameda County Hospital.

JEREMIAH STAMLER, M.D., (by invitation), Chicago, Ill.
Director, Heart Disease Control Program, Chicago Board of Health.

FREDRICK J. STARE, M.D., (by invitation), Boston, Mass.
Professor of Nutrition and Chairman of the Department, Harvard University School of Public Health.

CHARLES F. WILKINSON, JR., F.A.C.P., New York, N. Y.
Professor and Chairman of the Department of Medicine, New York University Post-Graduate Medical School.

The panel will deal with the role of foodstuffs in relation to atheroma, plasma lipids and thrombosis. The data from animal experiments, from regional studies of diet and disease, and from study of patients will be related to the management of patients.

Wednesday, April 22

11:30 A.M.–12:45 P.M.

PANEL P–8

Eighth Street Theatre

Electrocardiography—Problem Electrocardiograms.

Moderator: GEORGE E. BURCH, JR., F.A.C.P., New Orleans, La.
Henderson Professor of Medicine, Tulane University School of Medicine.

JOSEPH M. BARKER, F.A.C.P., Beverly Hills, Calif.
Clinical Associate Professor of Medicine (Cardiology), University of California School of Medicine at Los Angeles and University of Southern California School of Medicine.

JOHN S. GRAETTINGER, F.A.C.P., Chicago, Ill.
Associate Professor of Medicine, University of Illinois College of Medicine; Assistant Attending Physician and Director, Cardiorespiratory Division, Department of Medicine, Presbyterian Hospital.

FRANKLIN D. JOHNSTON, F.A.C.P., Ann Arbor, Mich.
Professor of Internal Medicine, University of Michigan Medical School.

The panel on electrocardiography will be concerned with a discussion of some of the more difficult problems in electrocardiography. It will consist of a question and answer type of panel in which we will ask the audience to submit questions and to enter into the discussions after each member of the committee presents, very briefly in an informal manner, some problems of importance.

Wednesday, April 22

11:30 A.M.–12:45 P.M.

PANEL P–9

Williford Room

The Serology of Collagen and Rheumatic Diseases.

Moderator: JOSEPH J. BUNIM, F.A.C.P., Bethesda, Md.
Associate Professor of Medicine, The Johns Hopkins University School of Medicine; Clinical Director, National Institute of Arthritis and Metabolic Diseases.

WILLIAM D. ROBINSON, F.A.C.P., Ann Arbor, Mich.
Professor of Internal Medicine, University of Michigan Medical School.

LAWRENCE E. SHULMAN, M.D., (by invitation), Baltimore, Md.
Assistant Professor of Medicine, The Johns Hopkins University School of Medicine.

GENE H. STOLLERMAN, F.A.C.P., Chicago, Ill.
Associate Professor of Medicine, Northwestern University Medical School.

Recent refinements in procedures, diagnostic significance, immunologic and pathogenetic implications of the L.E. test, the several current serologic tests for the "rheumatoid factor," the antistreptolysin titer and the chronic biologic false positive test for syphilis will be discussed in relation to systemic lupus erythematosus, collagen vascular disease, rheumatoid arthritis, systemic scleroderma, rheumatic fever and other connective tissue diseases.

Wednesday, April 22

11:30 A.M.–12:45 P.M.

PANEL P–10

Normandie Lounge

Plain Roentgen Film of the Abdomen: Uses and Pitfalls.

Moderator: PAUL C. HODGES, M.D., (by invitation), Chicago, Ill.
Emeritus Professor of Radiology, The University of Chicago, The School of Medicine.

WILLIAM R. EYLER, M.D., (by invitation), Detroit, Mich.
Radiologist-in-Chief, Henry Ford Hospital.

RICHARD K. GILCHRIST, M.D., (by invitation), Chicago, Ill.
Clinical Professor of Surgery (Rush), University of Illinois College of Medicine.

ROSCOE E. MILLER, M.D., (by invitation), Indianapolis, Ind.
Assistant Professor of Radiology, University of Indiana School of Medicine.

WALTER L. PALMER, F.A.C.P., Chicago, Ill.
Richard T. Crane Professor of Medicine, The University of Chicago, The School of Medicine.

This panel will be in the nature of a "stump the expert" quiz. Selected films unknown to the panel will be projected. The diagnostic advantages and disadvantages of plain films of the abdomen will be brought out by the discussion of the panel.

Wednesday, April 22

11:30 A.M.–12:45 P.M.

PANEL P–11

Waldorf Room

Myocardopathy—What, How, and Why?

Moderator: CLARENCE DE LA CHAPELLE, F.A.C.P., New York, N. Y.
Professor of Medicine, New York University Post-Graduate Medical School.

ALBERT I. RUBENSTONE, M.D., (by invitation), Chicago, Ill.
Assistant Professor of Pathology, University of Illinois College of Medicine.

LOUIS A. SELVERSTONE, (Associate), Boston, Mass.
Assistant Professor of Medicine, Tufts University School of Medicine.

GEORGE C. SUTTON, F.A.C.P., Evanston, Ill.
Assistant Professor of Medicine, Northwestern University Medical School.

Myocardopathy has seemed to connote various abnormalities to the clinicians, the pathologists, and certainly the patients. What it is, and how and when it occurs are several of the problems to be dealt with. Application of new techniques in its evaluation will be discussed.

Wednesday, April 22

11:30 A.M.–12:45 P.M.

PANEL P–12

Boulevard Room

Impact of Population Increase on Medicine.

Moderator: JOHN B. YOUMANS, F.A.C.P., Washington, D. C.
Dean Emeritus, Vanderbilt University School of Medicine; Technical Director of Research, Office of the Surgeon General, Department of the Army.

TALCOTT PARSONS, Ph.D., (by invitation), Cambridge, Mass.
Professor of Sociology, Department of Social Relations, Harvard University.

JOHN ROCK, M.D., (by invitation), Brookline, Mass.
Professor of Obstetrics, Harvard Medical School.

WALTER S. WIGGINS, F.A.C.P., Chicago, Ill.
Associate Secretary, Council on Medical Education and Hospitals, American Medical Association.

The discussion will cover the future growth of the population of the United States and the production of physicians to care for this increase. New medical schools will be needed. The age pattern of the United States will affect medical care. We need to control population growth. How will we do this?

Thursday, April 23

11:30 A.M.–12:45 P.M.

PANEL P–13

Blackstone Theatre

Follow-up after Cardiac Surgery.

Moderator: JAMES A. CAMPBELL, (Associate), Chicago, Ill.
Professor of Medicine, University of Illinois College of Medicine.

HARPER K. HELLEMS, M.D., (by invitation), Detroit, Mich.
Associate Professor of Medicine, Wayne State University College of Medicine.

ORMAND C. JULIAN, F.A.C.S. (by invitation), Chicago, Ill.
Clinical Associate Professor of Surgery, University of Illinois College of Medicine.

WILLIS J. POTTS, F.A.C.S., (by invitation), Chicago, Ill.
Professor of Surgery, Northwestern University Medical School.

A re-evaluation of the effectiveness of surgical treatment of heart disease will be undertaken. Particular attention will be directed to the "long term" follow-up of patients who have undergone surgery for either congenital or acquired lesions.

Thursday, April 23

11:30 A.M.–12:45 P.M.

PANEL P–14

Eighth Street Theatre

The Legitimate Uses of Adrenocortical Steroids.

Moderator: PHILIP S. HENCH, F.A.C.P., Rochester, Minn.
Professor of Medicine, University of Minnesota (Mayo Foundation).

SAMUEL M. FEINBERG, F.A.C.P., Chicago, Ill.
Professor of Medicine, Northwestern University Medical School.

JOSEPH W. JAILER, M.D., (by invitation), New York, N. Y.
Associate Professor of Medicine, Columbia University College of Physicians and Surgeons.

MARK H. LEPPER, F.A.C.P., Chicago, Ill.
Professor of Preventive Medicine, University of Illinois College of Medicine.

After 10 years of clinical experience with adrenocortical steroids indications and contra-indications to their use in various fields are emerging more clearly. The panel will emphasize their value and limitations in allergic, infectious, rheumatic and metabolic diseases.

Thursday, April 23

11:30 A.M.–12:45 P.M.

PANEL P–15

Williford Room

Renal Tubular Function and Dysfunction.

Moderator: ROBERT W. BERLINER, M.D., (by invitation), Bethesda, Md.
Associate Director (in charge of Research), National Heart Institute.

THEODORE N. PULLMAN, M.D., (by invitation), Chicago, Ill.
Associate Professor of Medicine, The University of Chicago, The School of Medicine.

WILLIAM B. SCHWARTZ, JR., (Associate), Boston, Mass.
Associate Professor of Medicine, Tufts University School of Medicine.

LOUIS G. WELT, F.A.C.P., Chapel Hill, N. C.
Professor of Medicine, University of North Carolina School of Medicine.

The discussion will deal with what is known about the functions of the renal tubules and the abnormalities of these functions which result from specific defects of renal tubular transport mechanisms and from physiologic disturbances and pharmacologic interventions.

Thursday, April 23

11:30 A.M.–12:45 P.M.

PANEL P–16

Normandie Lounge

The Adolescent and the Internist.

Moderator: T. WILLIAM LESTER, JR., M.D., (by invitation), Hinsdale, Ill.
Associate Professor of Medicine, The University of Chicago, The School of Medicine.

ROBERT D. HESS, Ph.D., (by invitation), Chicago, Ill.
Assistant Professor, Committee of Human Development, The University of Chicago.

ROBERT P. MASLAND, JR., M.D., (by invitation), Boston, Mass.
Associate Physician, Adolescent Unit, Children's Hospital.

CLIFTON C. RHEAD, JR., M.D., (by invitation), Chicago, Ill.
Clinical Assistant Professor of Phychiatry, University of Illinois College of Medicine.

The adolescent is too old to be considered a child and too young to be considered an adult. The chief problem is that he is not "considered." The panel will consider the problems of adolescence in detail—both emotional and organic and the role of the internist will be discussed, together with broader factors in our culture.

Thursday, April 23

11:30 A.M.–12:45 P.M.

PANEL P–17

Waldorf Room

The Treatment of Hemorrhagic Diseases.

Moderator: EUGENE L. LOZNER, F.A.C.P., Syracuse, N. Y.
Professor of Medicine, State University of New York College of Medicine at Syracuse.

WILLIAM DAMESHEK, F.A.C.P., Boston, Mass.
Professor of Medicine, Tufts University School of Medicine.

WILLIAM J. HARRINGTON, F.A.C.P., St. Louis, Mo.
Associate Professor of Medicine, Washington University School of Medicine.

MARIO STEFANINI, M.D., (by invitation), Boston, Mass.
Director of Research and Hematologist, St. Elizabeth's Hospital.

Discussion will include: (1) Idiopathic thrombocytopenic purpura; (2) Anaphylactoid purpura (non-thrombocytopenic),; (3) Disorders of first phase of blood coagulation, i.e., hemophilia and related disorders; (4) Disorders of second phase of coagulation, i.e., hypoprothrombinemia and related disorders.

Thursday, April 23

11:30 A.M.–12:45 P.M.

PANEL P–18

Boulevard Room

Diseases of Muscle Metabolism.

Moderator: DEREK E. DENNY-BROWN, M.D., (by invitation), Boston, Mass.
James Jackson Putnam Professor of Neurology, Harvard Medical School.

JOHN S. GARVIN, M.D., (by invitation), Chicago, Ill.
Assistant Professor of Neurology, University of Illinois College of Medicine.

LASZLO LORAND, Ph.D., (by invitation), Evanston, Ill.
Associate Professor of Chemistry, Northwestern University, Department of Chemistry, College of Liberal Arts and Sciences.

JACK METCOFF, M.D., (by invitation), Chicago, Ill.
Professor of Pediatrics, Northwestern University Medical School.

Metabolic processes in normal muscles will be outlined. Common and uncommon diseases of muscle will be discussed and their recognition, treatment and management will be briefly dealt with. The abnormalities of metabolism and disturbed physiology which develop in these diseases will be stressed.

Friday, April 24

11:30 A.M.–12:45 P.M.

PANEL P–19

Eighth Street Theatre

Progress Report on Hypertension.

Moderator: EDGAR V. ALLEN, F.A.C.P., Rochester, Minn.
Professor of Medicine, University of Minnesota (Mayo Foundation); Senior Consultant in Medicine, Mayo Clinic.

EDWARD D. FREIS, F.A.C.P., Washington, D. C.
Adjunct Clinical Professor of Medicine and Chief of Cardiovascular Research Laboratory and Hypertension Clinic, Georgetown University School of Medicine; Chief of Medical Service, Veterans Administration Hospital.

JOHN H. MOYER, III, (Associate), Philadelphia, Pa.
Professor of Medicine and Chairman of the Department of Internal Medicine, Hahnemann Medical College and Hospital of Philadelphia.

IRVINE H. PAGE, F.A.C.P., Cleveland, Ohio.
Professor of Medicine, Frank E. Bunts Educational Institute, and Director of Research, Cleveland Clinic Foundation.

Hypertension is an ever-present problem in general practice. In the past few years methods of treatment have been made available which for the most part are satisfactory. The panel will discuss the approach to the diagnosis of essential hypertension, indications for treatment and specific methods of treatment.

Friday, April 24

11:30 A.M.–12:45 P.M.

PANEL P–20

Williford Room

Questions and Answers in Diabetes.

Moderator: ALEXANDER MARBLE, F.A.C.P., Boston, Mass.
Assistant Professor of Medicine, Harvard Medical School.

GARFIELD G. DUNCAN, F.A.C.P., Philadelphia, Pa.
Professor of Medicine, University of Pennsylvania School of Medicine.

HARVEY C. KNOWLES, JR., (Associate), Cincinnati, Ohio.
Associate Professor of Medicine, University of Cincinnati College of Medicine.

RACHMIEL LEVINE, M.D., (by invitation), Chicago, Ill.
Professorial Lecturer in Physiology, The University of Chicago, The School of Medicine; Chairman, Department of Medicine, Michael Reese Hospital.

RANDALL G. SPRAGUE, F.A.C.P., Rochester, Minn.
Professor of Medicine, University of Minnesota (Mayo Foundation).

The panelists will attempt, in the light of present knowledge based on investigation and clinical experience, to answer questions regarding various aspects of diabetes, including the mode and site of action of insulin, choice of diet, the various types of insulin, the place of the oral hypoglycemic agents and the treatment of complications such as diabetic coma, neuropathy and peripheral vascular disease.

Friday, April 24

11:30 A.M.–12:45 P.M.

Panel P–21

Normandie Lounge

The Needle Biopsy—When and Why?

Moderator: HUGH H. HUSSEY, JR., F.A.C.P., Washington, D. C.
Dean and Professor of Medicine, Georgetown University School of Medicine.

MATTHEW H. BLOCK, M.D., (by invitation), Denver, Colo.
Associate Professor of Medicine, Division of Laboratory and Clinical Medicine, University of Colorado Medical Center.

SOL KATZ, F.A.C.P., Washington, D. C.
Adjunct Clinical Professor of Medicine, Georgetown University School of Medicine; Chief, Pulmonary Disease Division, District of Columbia General Hospital.

ROBERT C. MUEHRCKE, M.D., (by invitation), Chicago, Ill.
Instructor in Medicine, University of Illinois College of Medicine.

"Biopsy" formerly implied surgery. Now the needle pulls tissue from many places—liver, spleen, kidney, lung, pleura, bone marrow, even heart. This technique is a logical extension of the search for causes. Although it is a recent development, enough experience has been gained for an approach to "When and Why?"

Friday, April 24

11:30 A.M.–12:45 P.M.

PANEL P–22

Waldorf Room

Infections That are Hard to Treat.

Moderator: LOWELL A. RANTZ, F.A.C.P., San Francisco, Calif.
Professor of Medicine, Stanford University School of Medicine.

EDWIN D. KILBOURNE, (Associate), New York, N. Y.
Associate Professor of Public Health and Preventive Medicine and Director, Division of Virus Research, Cornell University Medical College.

VERNON KNIGHT, F.A.C.P., Nashville, Tenn.
Associate Professor of Medicine, Vanderbilt University School of Medicine.

RALPH R. TOMPSETT, F.A.C.P., Dallas, Tex.
Chief of Medicine, Baylor University Hospital.

Many serious infections that are difficult to manage are still encountered in spite of the brilliant success of antimicrobial therapy. The panel will emphasize the treatment of antibiotic resistant staphylococcal and gram negative bacillary disease, mixed bacterial infection, and severe fungus and viral disease.

Friday, April 24

11:30 A.M.–12:45 P.M.

PANEL P–23

Boulevard Room

Is There a Future to the Chemotherapy of Cancer?

Moderator: DAVID A. KARNOFSKY, M.D., (by invitation), New York, N. Y.
Associate Professor of Medicine, Cornell University Medical College; Associate Attending Physician, Chemotherapy Service, Department of Medicine, Memorial and James Ewing Hospitals; Member, Sloan-Kettering Institute.

WARREN H. COLE, F.A.C.S., (by invitation), Chicago, Ill.
Professor and Head, Department of Surgery, University of Illinois College of Medicine.

SAMUEL G. TAYLOR, III, F.A.C.P., Chicago, Ill.
Associate Clinical Professor of Medicine, University of Illinois College of Medicine.

CHARLES G. ZUBROD, M.D., (by invitation), Bethesda, Md.
Clinical Director, National Cancer Institute.

The panel members will discuss the present effectiveness of chemotherapy in several specialties and project what may be expected from chemotherapy in cancer in the near future. The discussion will include some of the newer chemotherapeutic agents.

THE CLINIC SESSIONS

COLOR TELEVISION OF MEDICAL CLINICS

Between 9:00 A.M. and 11:15 A.M. each day, Tuesday through Friday, clinics presented from the Michael Reese Hospital will be transmitted by closed circuit microwave to the television room on the Exhibition Floor. A new $9' \times 12'$ screen with three times the brightness and considerable gain in definition to the one used last year will be installed.

We are grateful for the cooperation of the distinguished clinicians who are participating in these clinics and for the technical guidance of Smith, Kline and French Laboratories of Philadelphia, whose sponsorship made this program possible.

Admission by registration badge; no tickets required.

Tuesday, April 21, 1959

Television Room, Exhibition Floor

Conrad Hilton Hotel

A.M.

9:00– 9:40 Hemoptysis.

PAUL H. HOLINGER, M.D., (by invitation), Chicago.

WILLIAM R. BARCLAY, M.D., (by invitation), Chicago.

Various types of conditions associated with hemoptysis will be presented, employing patients to illustrate pertinent aspects of the history and examina-

tion. Diagnostic techniques will be discussed and demonstrated, and differential diagnosis considered.

9:45–10:25 Diagnosis and Management of Pulmonary Insufficiency.
GORDON L. SNIDER, (Associate), Chicago.
DAVID W. CUGELL, (Associate), Chicago.

Pulmonary insufficiency will be defined, and there will be a demonstration of certain critical ventilatory tests. Following a discussion of etiology, the subject of therapy will be concisely reviewed.

10:30–11:15 Pulmonary Infection.
PAUL S. RHOADS, F.A.C.P., Chicago.
MARK H. LEPPER, F.A.C.P., Chicago.

Certain of the diagnostic features of important types of pulmonary infection will be presented, using patients, and the role of bacteriologic study emphasized. The selection and use of antibacterial agents, as well as their improper use, will be reviewed, and their place in relation to other supportive measures indicated.

THE TELEVISION CLINIC SESSIONS

Wednesday, April 22, 1959

Television Room, Exhibition Floor

Conrad Hilton Hotel

A.M.

9:00– 9:40 Diagnostic Techniques in Pancreatic Disease.
JOSEPH B. KIRSNER, F.A.C.P., Chicago.
HEINRICH NECHELES, F.A.C.P., Chicago.
HOWARD F. RASKIN, M.D., (by invitation), Chicago.

Clinical problems in types of pancreatic disease will be presented, using patients, with particular emphasis on the role of diagnostic tests.

9:45–10:25 The Patient with Hepatomegaly.
RICHARD B. CAPPS, F.A.C.P., Chicago.
ROBERT M. KARK, F.A.C.P., Chicago.

The discussion will center around the clinical significance and differential diagnosis of hepatomegaly. The relative importance of the history, physical findings, laboratory tests and liver biopsy under different circumstances will be emphasized, and patients will be shown illustrating certain of the points presented.

10:30–11:15 Gross Hematemesis.
WALTER L. PALMER, F.A.C.P., Chicago.
JOHN T. REYNOLDS, F.A.C.S., (by invitation), Chicago.

The diagnostic approach to the patient with gross hematemesis will be considered, using patients, and techniques in differential diagnosis considered and reviewed. The role of medical and surgical management of certain of the conditions associated with gross hematemesis will be illustrated and discussed, both from the point of view of their applicability and their limitations.

THE TELEVISION CLINIC SESSIONS

Thursday, April 23, 1959

Television Room, Exhibition Floor

Conrad Hilton Hotel

A.M.

9:00– 9:40 Renal Infection.

GEORGE GEE JACKSON, (Associate), Chicago.
ADRIAN M. OSTFELD, M.D., (by invitation), Chicago.
EDWARD H. KASS, M.D., (by invitation), Boston.

Medical as well as surgical aspects of acute and chronic renal infection will be considered, and patients shown to demonstrate certain of the clinical problems discussed. The bacteriologic aspects of renal infection will be particularly presented and implications for effective therapy reviewed.

9:45–10:25 Diagnostic Techniques in Renal Disease.

JACK METCOFF, M.D., (by invitation), Chicago.
ROBERT C. MUEHRCKE, M.D., (by invitation), Chicago.
VICTOR E. POLLAK, M.D., (by invitation), Chicago.

There will be a demonstration and discussion of certain diagnostic techniques employed in the definition and identification of renal disease. These will include techniques for examination of the urine, certain key renal function tests, radiologic evaluation, and the role and application of renal biopsy.

10:30–11:15 The Nature of Nephritis.

DAVID P. EARLE, JR., F.A.C.P., Chicago.
ROBERT B. JENNINGS, M.D., (by invitation), Chicago.

The natural history of the various phases of post-streptococcal glomerulonephritis will be illustrated by consideration of several typical patients. Techniques for diagnosis, prognosis and management in these specific instances will be emphasized. Nephritis of non-streptococcal origin will be contrasted with these patients, with special attention being paid to renal diseases characterized by the nephrotic syndrome. An attempt will be made to present a classification of nephritis in a way that will assist in the practical management of patients.

THE TELEVISION CLINIC SESSIONS

Friday, April 24, 1959

Television Room, Exhibition Floor

Conrad Hilton Hotel

A.M.

9:00– 9:40 Open Heart Surgery.

BENJAMIN M. GASUL, F.A.C.P., Chicago.
F. JOHN LEWIS, F.A.C.S., (by invitation), Chicago.
ROBERT A. MILLER, M.D., (by invitation), Chicago.

Following an introductory presentation of the new field of open heart surgery, there will be a discussion of indications for surgery in ventricular septal defects. This will be followed by a review of the indications for open heart surgery in other congenital lesions. Finally, there will be a demonstration and explanation of actual heart-lung machines, with description of operative techniques.

9:45–10:25 Treatment of Lymphoma and Leukemia.

HOWARD L. ALT, F.A.C.P., Chicago.
LOUIS R. LIMARZI, F.A.C.P., Chicago.

The place of established and newer methods of treatment of lymphoma and leukemia will be reviewed, with particular reference to their application in patients who will be presented. The limitations and results of these forms of treatment will be considered, with their usefulness for the practicing physician.

10:30–11:15 Endocrine Surgery and Steroids in Malignant Disease.

SAMUEL G. TAYLOR, III, F.A.C.P., Chicago.
DANELY P. SLAUGHTER, F.A.C.S., (by invitation), Chicago.
WM. M. S. IRONSIDE, M.D., (by invitation), Chicago.

This will be a case presentation demonstrating tumor regression in breast cancer from estrogens, androgens, oophorectomy, hypophysectomy and adrenalectomy. The effect of corticoids will also be discussed. This will be followed by a discussion of the surgical technique and the mortality and morbidity of the surgical procedures, and the advantages of surgical oophorectomy over radiation castration. Data will be presented on the relative effectiveness of these procedures and what can be expected from the point of view of longevity, palliation and actual tumor regression.

THE CLINIC SESSIONS

CLINICS AT HOSPITALS

The regular Hospital Clinics will be conducted on Tuesday and Thursday from 9:00 A.M. to 11:00 A.M. **Admission to the Hospital Clinics will require special tickets,** which will be issued to MEMBERS in advance of the Session and to NON-MEMBERS directly at the Registration Bureau in the Conrad Hilton Hotel. Application forms for tickets for the Hospital Clinics and Panel Discussions are sent to all members with the program.

The Committee on Clinics is committed to a program of clinics in the true sense of that term—patients will be shown and discussed. A wide range of medical topics important to the clinician is offered.

The Committee on Transportation recommends the use of taxicabs for reaching the Hospital Clinics, and will arrange for an adequate number of taxicabs to be available also for the return trip.

Members are requested not to attempt to split clinics with one another. Tickets will be required for each and every one of the Hospital Clinics, unless specifically otherwise mentioned. The co-operation of every one in securing his clinic tickets will assist greatly in distributing the attendance according to the capacity of each meeting room. It is self-evident that a clinic arranged for fifty will lose its value for all if a hundred crowd in. Ticket registration, naturally, is the only effective method for keeping the attendance within the capacities indicated.

Member registration blanks for the clinics should be filled out and returned to the Executive Secretary promptly. Upon receipt at the College Office, proper tickets will be selected and held at the Registration Bureau in the Conrad Hilton Hotel, or, on the request of the member, will be mailed to him. Reservations by mail cannot be made after April 1, but reservations may be made in person at the Registration Bureau on the afternoon preceding any clinic day, providing tickets are still available.

Members who reserve clinic tickets are urgently requested to notify the Executive Secretary, and to return their tickets, if they find they will be unable to attend.

Hospital Clinic Transportation Directions

While the Committee on Transportation has recommended that taxicabs be used for reaching the various hospital clinics, it has also prepared the following directions:

West Side

The Cook County Hospital is located at 1835 West Harrison Street. Harrison Street buses, southbound on State Street, may be boarded at the northwest corner of State and Harrison which is one block north and two blocks west of the Conrad Hilton Hotel. Alight at the Hospital.

Mount Sinai Hospital at 2750 West 15th Place is conveniently served by the Ogden Avenue bus. Board a southbound Cottage Grove #4 bus on Wabash Avenue and transfer west on Roosevelt Road and ride to Ogden Avenue. Transfer to the westbound Ogden Avenue bus and alight at California. Walk south a few steps to the Hospital.

South Side

The Billings Hospital is located at 950 East 59th Street, two blocks east of Cottage Grove Avenue and is served by Cottage Grove route #4 buses which may be boarded on Wabash Avenue at 8th Street, just one block west of the Conrad Hilton Hotel.

North Side

Wesley Memorial Hospital is conveniently served by the Ohio-Depots route #157 bus which operates on Fairbanks Court at Superior. Board a northbound Jeffery #5 or a South Park #3 bus on Michigan Avenue and alight at the Randolph Street stop. At that point, transfer to a northbound Ohio-Depots route #157 bus to Fairbanks Court and Superior Street, where the Hospital is located.

PROGRAM OF HOSPITAL CLINICS

Tuesday, April 21, 1959, 9:00 A.M.–11:00 A.M.

A ALBERT MERRITT BILLINGS HOSPITAL

950 East 59th Street

Room P-117

(Capacity: 240)

WALTER L. PALMER, Moderator

CRITICAL PROBLEMS IN GASTROENTEROLOGY:
(with case presentations)

1. The Cytologic Diagnosis of Gastrointestinal Cancer.
   HOWARD F. RASKIN.
2. Gastric Ulcer: Definitive Diagnosis and Therapy.
   WALTER L. PALMER.
3. Ulcerative Colitis: Problems in Management.
   JOSEPH B. KIRSNER.
4. Steatorrhea—steroids, antibiotics or the gluten free diet?
   JEAN A. SPENCER.
5. Post-Cholecystectomy Problems.
   CHARLES B. CLAYMAN.

B CHICAGO WESLEY MEMORIAL HOSPITAL

250 East Superior Street

1st Floor Conference Room

(Capacity: 100)

FREDERICK A. LESTINA, Moderator

METABOLIC AND ENDOCRINE CLINIC:

1. Congenital Hypoparathyroidism.
   SMITH FREEMAN, RICHARD F. HERNDEN and PAUL C. BUCY.
2. Sheehan's Syndrome.
   SMITH FREEMAN, UROSH L. SEFFER, RONALD R. GREENE and EMERY G. GRIMM.
3. Adrenocortical Hyperfunction.
   SMITH FREEMAN, ROBERT T. MARSHALL, M. META KUNDE and VINCENT J. O'CONOR.

4. Addison's Disease Plus Diabetes.
FREDERICK A. LESTINA, JAMES B. HURD, EMERY G. GRIMM and UROSH L. SEFFER.

C

COOK COUNTY HOSPITAL

1835 West Harrison Street

Medical Amphitheater

(Capacity: 140)

GEORGE W. HOLMES, Moderator

CURRENT DIAGNOSTIC METHODS USED IN CHEST DISEASES:

1. Pleural and Scalene Biopsies.
PAUL B. SZANTO.
2. Non-tuberculous and Fungi Bacteriological Findings.
DANIEL S. KUSHNER.
3. General and Tuberculous Bacteriology.
GEORGE METZGER.
4. Pulmonary Heart Diseases.
DAVID W. CUGELL.
5. Angiocardiographic Findings.
WILLIAM B. BUCKINGHAM.
6. Physiological Studies and Catheterization Findings.
AIDA BALTAZAR.
7. Radiation Therapy.
IRVIN F. HUMMON, JR.
8. Diagnostic Radiological Findings.
WILLIAM MESZAROS.
9. Esophageal Diseases.
SAMUEL HYMAN.

D

EVANSTON HOSPITAL

Clinics to be Presented

at

SHERATON-BLACKSTONE HOTEL

South Michigan Avenue & East Balbo Drive

Hubbard Room

(Capacity: 150)

ERNEST G. McEWEN, Moderator

9:00 A.M.–10:00 A.M. MEDICAL SHOCK.

The causes, mechanism of production, and management of medical shock will be demonstrated by the presentation of unusual clinical problems.

ROBERT P. GILBERT and BERNARD H. ADELSON.

10:00 A.M.–11:00 A.M. THE MANAGEMENT OF REFRACTORY EDEMA.

The control of refractory edema will be discussed and interesting patients illustrating various types of problems will be presented.

GEORGE C. SUTTON and WILLIAM P. McKEEVER.

F

MERCY HOSPITAL

2537 South Prairie

John B. Murphy Amphitheater

(Capacity: 200)

HENRY L. SCHMITZ, Moderator

PROSTHETIC APPLIANCES IN THE MANAGEMENT OF AORTIC INSUFFICIENCY.

JACK VAN ELK and JOHN L. KEELEY.

BODY COMPOSITION IN CONGESTIVE HEART FAILURE.

PETER J. TALSO and GEORGE W. FERENZI.

G

MICHAEL REESE HOSPITAL

2929 South Ellis Avenue

Rothschild Auditorium

(Capacity: 250)

9:00 A.M.–10:00 A.M.

LOUIS N. KATZ, Moderator

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF PAROXYSMAL TACHYCARDIAS:

Paroxysmal Tachycardia of Undetermined Origin.
JACOB S. GOLDEN.

Adams-Stokes Syndrome due to Paroxysmal Ventricular Tachycardia and Transient Ventricular Fibrillation.
RICHARD LANGENDORF.

Paroxysmal Tachycardias in Ventricular Pre-excitation (WPW).
ALFRED PICK.

10:00 A.M.–11:00 A.M.

AARON M. JOSEPHSON, Moderator

GENETIC DISTURBANCES OF HEMOGLOBIN METABOLISM:

Homozygous Hemoglobin S. Disease.
ERNEST MOND.

Homozygous Hemoglobin C and C Plus S. Disease.
ARTHUR A. BILLINGS.

Thalassemic Syndromes.
AARON M. JOSEPHSON.

H

MOUNT SINAI HOSPITAL

2750 West 15th Place

Leopold Kling Auditorium

(Capacity: 300)

9:00 A.M.–10:00 A.M.

MARTIN M. KIRSHEN, Moderator

UNUSUAL MANIFESTATIONS OF LYMPHOMA:

Two case reports of unusual gastrointestinal and immuno-hematological manifestations of lymphoma.

Immuno-hematology.
ISRAEL DAVIDSOHN.

Pathology.
HENRY RAPPAPORT.

Clinical Gastroenterological Aspects.
JEROME NADELHAFT.

Experimental Concepts.
PHILIPPE SHUBIK.

10:00 A.M.–11:00 A.M.

GEORGE C. COE, Moderator

DISTURBANCES IN PLASMA PROTEINS:

Cases to include:
Rheumatoid Arthritis with Positive Lupus Preparation.
Boeck's Sarcoid.
Hypogammaglobulinemia.

Plasma Proteins in Collagen Diseases.
EMANUEL E. MANDEL.

Biochemical Aspects of Sarcoidosis.
HARRY F. WEISBERG.

The Rheumatoid Factor.
ARNOLD BLACK.

The L. E. Factor.
IRVING A. FRIEDMAN.

Hypogammaglobulinemia.
AARON GROSSMAN.

J

PASSAVANT MEMORIAL HOSPITAL

303 East Superior Street

Auditorium

(Capacity: 130)

HOWARD L. ALT, Moderator

CLINIC ON DISEASES OF THE BLOOD:

9:00 A.M. Refractory Anemia.
HOWARD L. ALT.

9:30 A.M. Lymphoma.
WALTER A. RAMBACH.

10:00 A.M.–11:00 A.M.

CLINIC ON RHEUMATIC DISEASES
GENE H. STOLLERMAN and FRANK R. SCHMID

K

PRESBYTERIAN–ST. LUKE'S HOSPITAL

1753 West Congress Street

Albert B. Dick Amphitheater

(Capacity: 200)

SAMUEL G. TAYLOR, III, Moderator

THERAPEUTIC OPPORTUNITIES FOR THE INTERNIST IN THE MANAGEMENT OF METASTATIC MALIGNANCY:

Chemotherapy.
SYDNEY KOFMAN.

Blood Dyscrasias Secondary to Treatment.
FRANK E. TROBAUGH, JR.

Endocrine Therapy.
CHARLES PERLIA.

Biochemical Rationale and Evaluation of Therapy.
HOWARD SKY-PECK.

L

RESEARCH AND EDUCATIONAL HOSPITALS

UNIVERSITY OF ILLINOIS

1859 West Polk Street

Room 106, D.M.P. Building

(Capacity: 190)

FORD K. HICK, Moderator

INFECTIOUS DISEASE ROUNDS—Including:

Meningitis.
Respiratory Diseases Due to Viruses.
Problem of Penicillin.
Resistant Staphylococci and Observations on Newer Antibiotics.

HARRY F. DOWLING, MARK H. LEPPER and GEORGE GEE JACKSON.

M

ST. LUKE'S HOSPITAL

1439 South Michigan Avenue

Main 3 Conference Room

(Capacity: 150)

WALTER F. HOEPPNER, Moderator

PROBLEMS IN DIABETES:

Disturbances in Fat Metabolism.
EDWIN F. HIRSCH.

Neurological Complications.
ROLAND P. MACKAY.

Diabetic Retinopathies.
JAMES F. W. CLARK and CHESTER COGGESHALL.

LIVER DISEASE:

Clinical Significance of Jaundice.
RICHARD B. CAPPS.

Relationship between the Liver and the Brain.
PHILIP N. JONES.

Partial Hepatectomy.
JOHN T. REYNOLDS.

N

VETERANS ADMINISTRATION RESEARCH HOSPITAL

330 East Huron Street

Room A-405

(Capacity: 150)

CRAIG W. BORDEN, Moderator

FREQUENTLY ENCOUNTERED PROBLEMS IN ELECTROLYTE BALANCE:

Respiratory Acidosis.
CRAIG W. BORDEN and STANFORD K. SWEANY.

Hypokalemic Alkalosis.
GEORGE C. HENEGAR and MORRIS A. LIPTON.

Acute Renal Failure.
W. JAMES KUHL, JR., and FRANCIS J. HADDY.

O

VETERANS ADMINISTRATION
WEST SIDE HOSPITAL

820 South Damen Avenue

Auditorium

(Capacity: 250)

ROY J. KORN, Moderator

COMMON AND UNUSUAL FEATURES OF CIRRHOSIS:

1. Correlation of Clinical, Biochemical and Histologic Aspects.
2. Types of Anemia Associated with Cirrhosis.
3. Coagulation Defects Associated with Cirrhosis.
   HYMAN J. ZIMMERMAN, BERNHARD CHOMET, PAUL HELLER and SHELDON E. KRASNOW.

Thursday, April 23, 1959, 9:00 A.M.–11:00 A.M.

A

ALBERT MERRITT BILLINGS HOSPITAL

950 East 59th Street

Room P-117

(Capacity: 240)

HENRY T. RICKETTS, Moderator

STEROIDS—THEIR BENEFITS AND DANGERS:

(with case presentations)

1. Steroid Induced Connective Tissue Reactions.
   ATTALLAH KAPPAS.
2. Biopsy Studies of Lupus Nephritis on Steroid Treatment.
   JOHN D. ARNOLD.
3. Intractable Asthma.
   DAVID W. TALMAGE.
4. Treatment of Dermatitis.
   ALLAN L. LORINCZ.
5. Role of Steroids in Chronic Lung Disease.
   BENJAMIN BURROWS.

B

CHICAGO WESLEY MEMORIAL HOSPITAL

250 East Superior Street

1st Floor Conference Room

(Capacity: 100)

WILSON H. HARTZ, JR., Moderator

METABOLIC DEFECTS:

1. Hemochromatosis.
   JOSEPH H. ROBBINS, BETTY HAHNEMAN and THOMAS C. LAIPPLY.
2. Hepatolenticular Degeneration.
   BENJAMIN BOSHES, ROBERT T. MARSHALL and RICHARD A. PERRITT.
3. Carcinoid.
   W. WALTER SITTLER, MICHAEL GOVOSTIS and FRANCIS J. HADDY.
4. Zollinger-Ellison Syndrome.
   ROGER W. FRISKEY, PAUL S. RHOADS, WALTER G. MADDOCK and JOHN H. ANNEGERS.

C

COOK COUNTY HOSPITAL

1825 West Harrison Street

Medical Amphitheater

(Capacity: 140)

FREDERICK STEIGMANN, Moderator

SEMINAR ON LIVER DISEASE:

1. Case Presentation.
   RESIDENT in MEDICINE.
2. Biochemical Changes in Liver Disease.
   ALVIN DUBIN.
3. Hepatic Blood Flow in the Diagnosis of Liver Disease.
   SHELDON S. WALDSTEIN.
4. Massive Bleeding in Liver Disease; Diagnostic and Therapeutic Considerations.
   JOHN R. TOBIN, JR.
5. Peritoneoscopy as a Diagnostic Aid.
   FERNANDO VILLA.
6. Hepatic Coma.
   RICHARD B. TERRY.

D

EVANSTON HOSPITAL

Clinics to be Presented

at

SHERATON-BLACKSTONE HOTEL

South Michigan Avenue & East Balbo Drive

Hubbard Room

(Capacity: 150)

LEONARD F. JOURDONAIS, Moderator

9:00 A.M. The Present Picture of Poliomyelitis.
MARTIN H. SEIFERT.

9:30 A.M. Infectious Mononucleosis.
HARRY B. HARDING.

10:00 A.M. Geriatrics—Surgical Indications in the Aged.
ARNOLD L. WAGNER, GEORGE C. TURNBULL and STEPHEN E. REID.

E HINES VETERANS ADMINISTRATION HOSPITAL

Presented at

VETERANS RESEARCH HOSPITAL

330 East Huron Street

Room A-405

(Capacity: 150)

LYLE A. BAKER, Moderator

CERTAIN CLINICAL ASPECTS OF RHEUMATIC DISEASES:

1. The L. E. Phenomenon in Rheumatoid Arthritis.
ARNOLD BLACK.
2. Rheumatoid Spondylitis.
ANGELO TOIGO and EVAN M. BARTON.
3. Reiter's Syndrome.
MAX M. MONTGOMERY.
4. Some Complications of ACTH and Steroid Therapy.
ROBERT M. POSKE.

G MICHAEL REESE HOSPITAL

2929 South Ellis Avenue

Rothschild Auditorium

(Capacity: 250)

9:00 A.M.–10:00 A.M.

RACHMIEL LEVINE, Moderator

SYNDROMES OF HYPERADRENAL CORTICALISM:

Cushing's Syndrome.
ROBERT C. LEVY.

Primary Aldosteronism.

The Adrenogenital Syndrome.
JAY J. GOLD.

10:00 A.M.–11:00 A.M.

DAVID H. ROSENBERG, Moderator

REGIONAL ENTERITIS:

Pathologic Physiology.
HEINRICH NECHELES.

Recurrent Regional Enteritis and Its Sequelae.
DAVID H. ROSENBERG.

Medical Management of Regional Enteritis, with Emphasis on the Value of Steroids.
MITCHELL A. SPELLBERG.

H

MOUNT SINAI HOSPITAL

2750 West 15th Place

Leopold Kling Auditorium

(Capacity: 300)

9:00 A.M.–10:00 A.M.

HYMAN J. ZIMMERMAN, Moderator

CORRELATION OF STRUCTURE AND FUNCTION IN DISEASE:

Series of short case presentations illustrating correlation of structure, clinical and laboratory data, including: Liver, Kidney, Thyroid, Pancreas, Lung.

Biochemical Aspects.
EMANUEL E. MANDEL.

Pathology.
LEO KRAINER.

Liver and Pancreas.
ERWIN M. KAMMERLING.

Respiratory.
JOSEPH K. FREILICH.

Thyroid.
ALBERT J. LEVINE.

Renal.
SEYMOUR FISHKIN.

10:00 A.M.–11:00 A.M.

HARRY J. ISAACS, Moderator

ENZYME ABNORMALITIES IN DISEASE:

Series of short case presentations.

Patterns of Enzymatic Abnormalities in Hepatic Disease.
HYMAN J. ZIMMERMAN.

Patterns of Enzymatic Abnormalities in Hematologic Conditions.
MICHAEL WEST.

Patterns of Enzymatic Abnormalities in Cardiac Diseases.
HYMAN J. B. HIRSHFIELD.

The Plasma Lipolytic System.
SAUL P. BAKER.

J

PASSAVANT MEMORIAL HOSPITAL

303 East Superior Street

Auditorium

(Capacity: 130)

GERRY A. SMYTH, Moderator

CLINIC ON CARDIOVASCULAR DISEASE:

Surgery of Interatrial Septal Defects.
F. JOHN LEWIS.

Primary Pulmonary Hypertension.
HUGH A. FLACK.

Ebstein's Anomaly.
PAUL KEZDI.

A Post-Infarction Syndrome.
GERRY A. SMYTH.

The Esophageal Electrocardiogram in the Diagnosis of Cardiac Arrhythmias.
WILLIAM H. WEHRMACHER.

Extra Cardiac Factors in Coronary Artery Disease.
CHAUNCEY C. MAHER.

K

PRESBYTERIAN-ST. LUKE'S HOSPITAL

1753 West Congress Street

Albert B. Dick Amphitheater

(Capacity: 200)

THEODORE B. SCHWARTZ, Moderator

PROBLEMS IN DIAGNOSIS AND MANAGEMENT OF DISORDERS OF CALCIUM METABOLISM:

Osteoporosis.
ROBERT D. RAY.

Phosphate-wasting Nephropathy.
ROBERT E. DEDMON.

Pathophysiology of Parathyroid Disease.
GORDON STEWART.

Secondary Hypoparathyroidism.
VICTOR E. POLLAK.

L

RESEARCH AND EDUCATIONAL HOSPITALS
UNIVERSITY OF ILLINOIS

1859 West Polk Street

Room 106, D.M.P. Building

(Capacity: 190)

NORMAN B. ROBERG, Moderator

CARDIOVASCULAR RENAL CLINICS:

Post-myocardial Infarction Syndrome.
LOUIS FELDMAN.

Valvular Insufficiency.
HARRY A. BLISS.

Accurate Diagnosis of the Nephrotic Syndrome.
ROBERT M. KARK.

Pyelonephritis and Hypertension.
HANS GRIEBLE.

M

ST. LUKE'S HOSPITAL

1439 South Michigan Avenue

Main 3 Conference Room

(Capacity: 150)

9:00 A.M.–10:00 A.M.

THOMAS J. COOGAN, Moderator

CARDIOPULMONARY PHYSIOLOGY:

Emphysema, Asthma, Cor Pulmonale and Pulmonary Hypertension.
ALBERT H. ANDREWS, JR., and OLDRICH PREC.

10:00 A.M.–11:00 A.M.

SURGERY OF THE CARDIOVASCULAR SYSTEM.
ORMAND C. JULIAN and WILLIAM S. DYE.

O

VETERANS ADMINISTRATION
WEST SIDE HOSPITAL

820 South Damen Avenue

Auditorium

(Capacity: 250)

9:00 A.M.–10:00 A.M.

PAUL HELLER, Moderator

CLINICAL SIGNIFICANCE OF HETEROZYGOUS STATE IN HEMOGLOBINOPATHIES.

AARON M. JOSEPHSON and LOUIS R. LIMARZI.

10:00 A.M.–11:00 A.M.

CLINICAL SIGNIFICANCE OF PLEURAL BIOPSIES.

ALVIN SOMBERG, WILLIAM F. T. KELLOW and BERNHARD CHOMET.

In smooth muscle spasm...

• controls *stress*

• relieves *distress*

Pro-Banthine® with Dartal®

Pro-Banthine—
unexcelled for relief of cholinergic spasm—
has been combined with
Dartal—
new, well-tolerated agent for stabilizing emotions—
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Pro-Banthine with Dartal—
for more specific control of functional gastrointestinal disorders, especially those aggravated by emotional tension.

Specific Clinical Applications: Functional gastrointestinal disturbances, pylorospasm, peptic ulcer, gastritis, spastic colon (irritable bowel), biliary dyskinesia.

Dosage: One tablet three times a day.

Availability: Aqua-colored tablets containing 15 mg. of Pro-Banthine (brand of propantheline bromide) and 5 mg. of Dartal (brand of thiopropazate dihydrochloride). G. D. Searle & Co., Chicago 80, Illinois. Research in the Service of Medicine.

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- *documented effectiveness and safety[1,2,3]*

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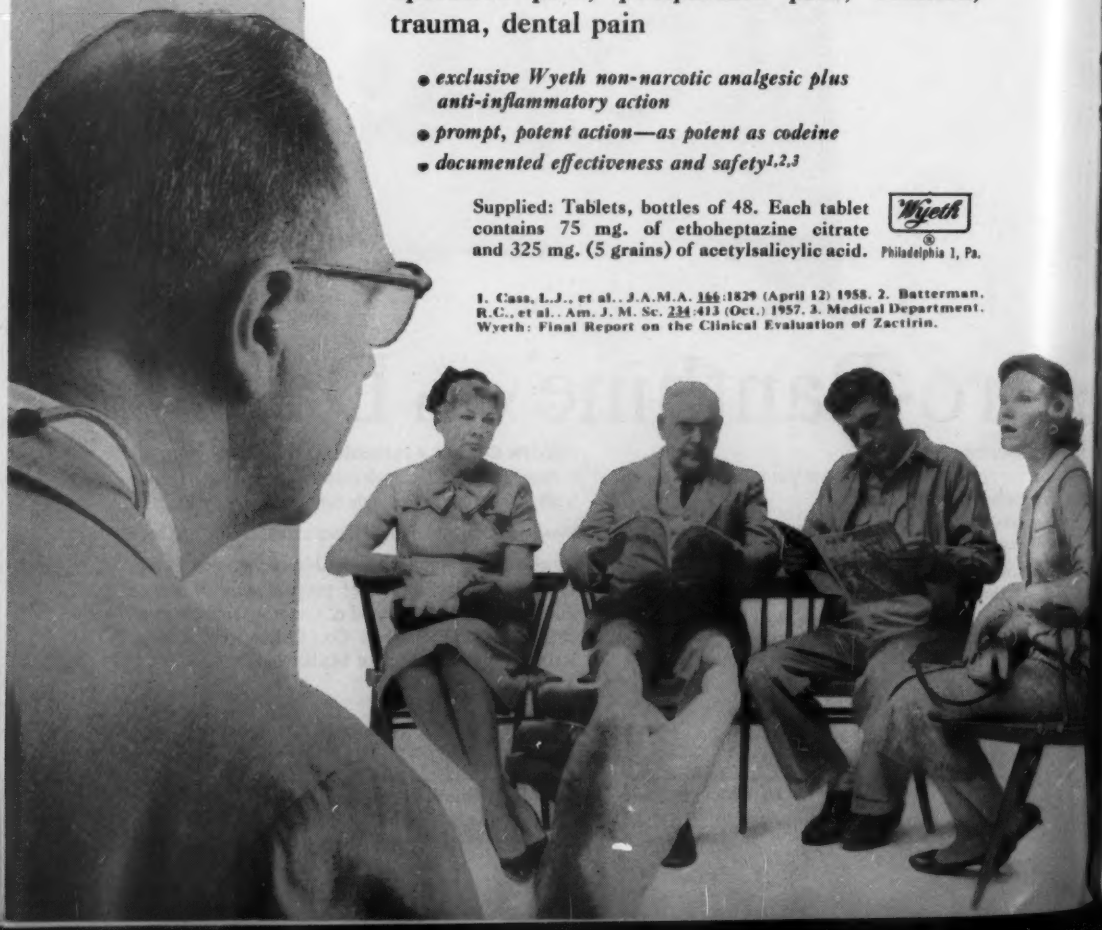
1. Cass, L.J., et al.. J.A.M.A. 166:1829 (April 12) 1958. 2. Batterman, R.C., et al.. Am. J. M. Sc. 234:413 (Oct.) 1957. 3. Medical Department, Wyeth: Final Report on the Clinical Evaluation of Zactirin.



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Improved blood flow to the myocardium, after a coronary thrombosis, promotes development of essential collateral circulation, thereby helping to repair damage.

Peritrate, 20 mg. q.i.d., safely increases coronary blood supply without appreciably changing blood pressure or pulse rate. Its routine use in management of the post-coronary patient will provide safe, effective vasodilatation and prevent anginal attacks often encountered in the convalescent period.

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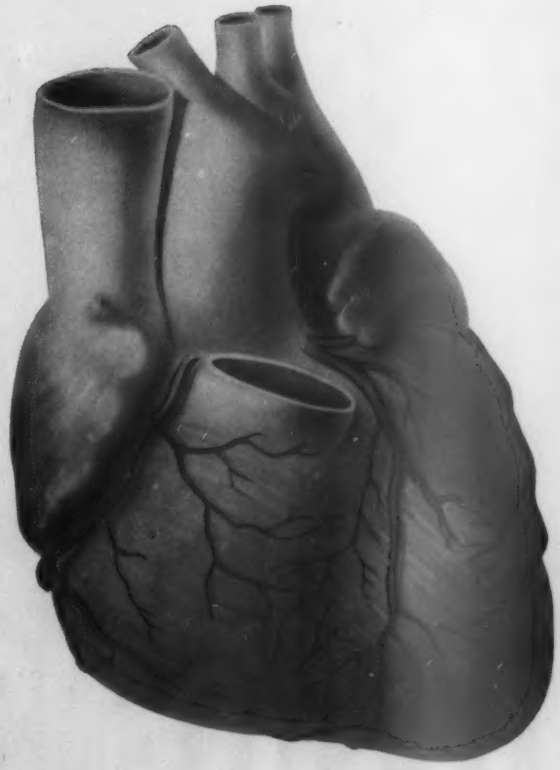
MORRIS PLAINS, N. J.



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Reinhardt, D. J.:
Delaware State Med. J. 30:1, January 1958.

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Bunn, W. H., Jr.:
Ohio State Med. J. 54:1168, September 1958.

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". . . it seems desirable to add potassium chloride 4 Gm. per day . . . in cases of hypertension. . . ."

Herrmann, G. R., Hejtmancik, M. R., Graham, R. N. and Marburger, R. C.:
Texas State J. Med. 54:639, September 1958.

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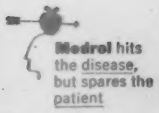

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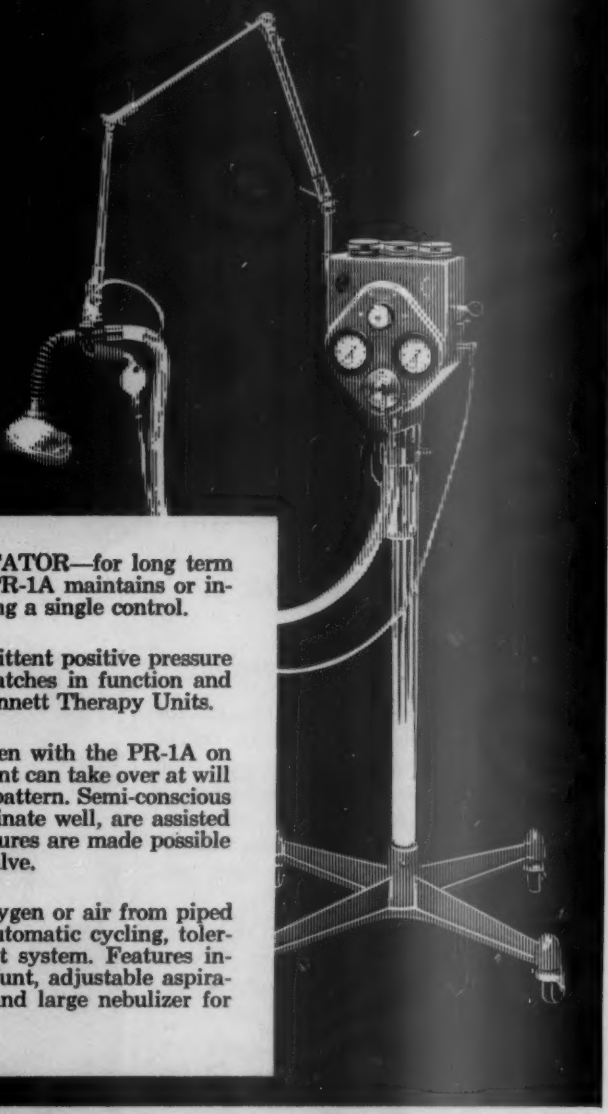

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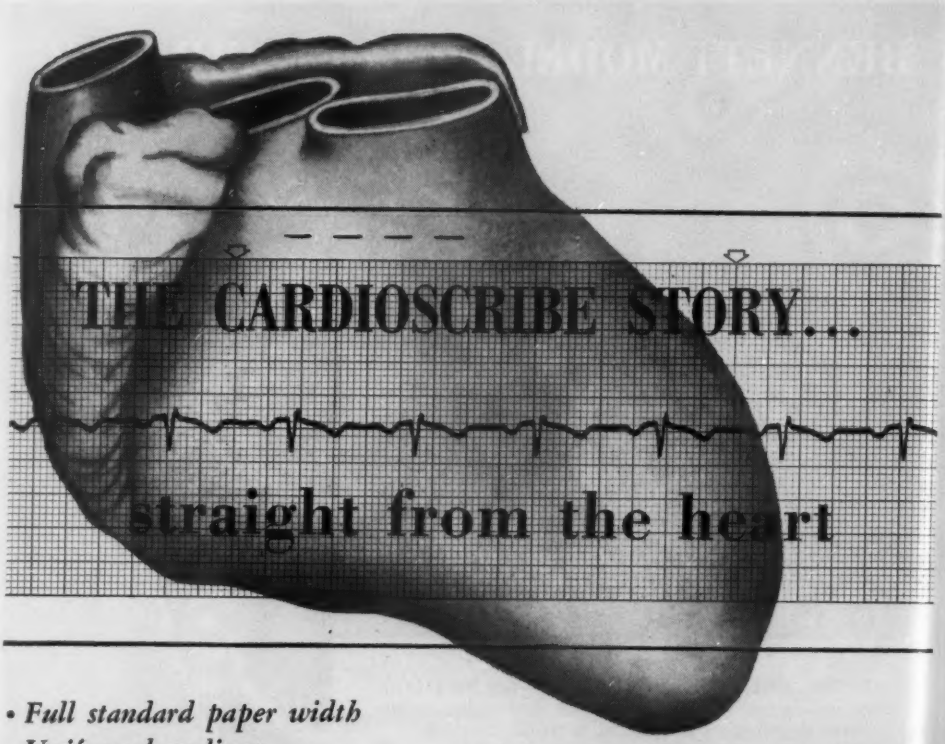

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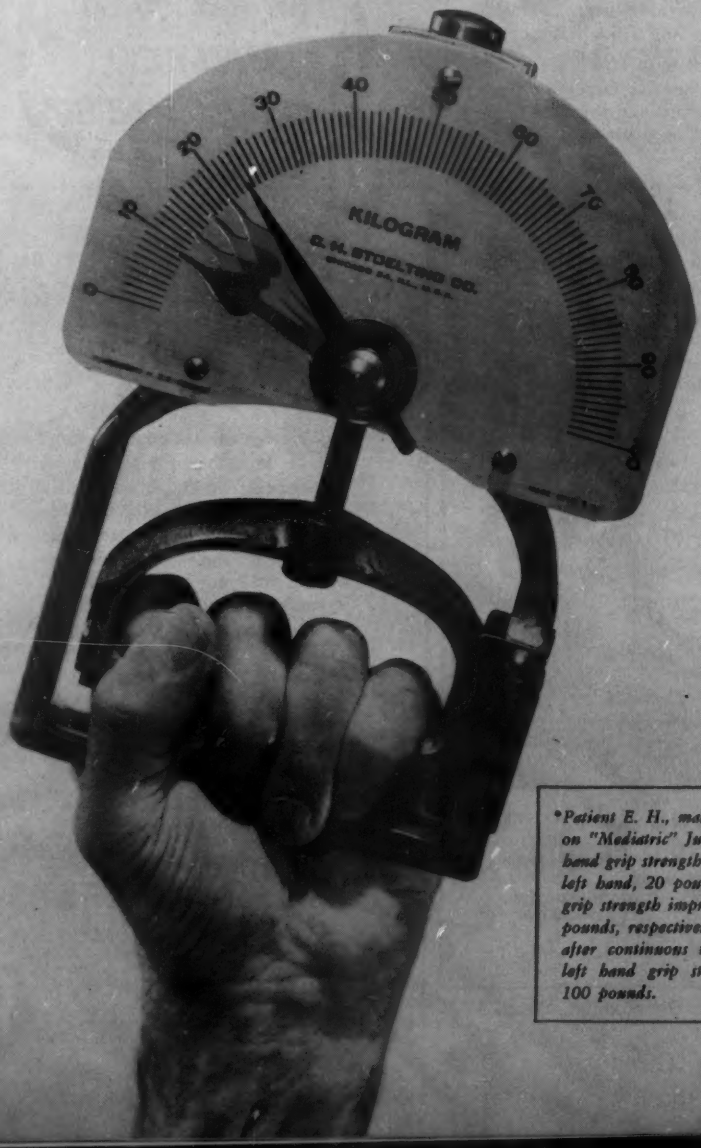

*Patient E. H., male, age 88, started on "Mediatric" July 24, 1952. Right hand grip strength measured 32 pounds, left hand, 20 pounds. Six weeks later, grip strength improved to 62 and 52 pounds, respectively. On June 29, 1954, after continuous therapy both right and left hand grip strength registered 100 pounds.

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1. Perlman, S. M., and Davidson, J. M.: *Presented before the Third Congress of the International Association of Gerontology, London, England, July 19-23, 1954.*

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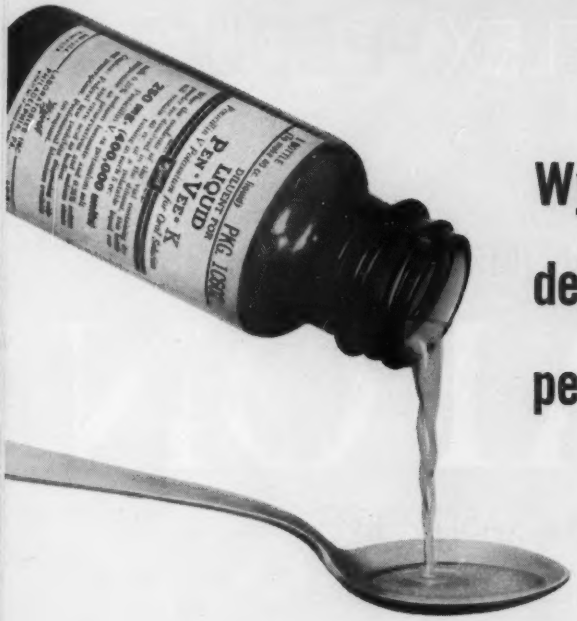

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1. Miller, J. H., et al.: Am. J. Dig. Dis. 3:229-231, 1958. 2. Swartzwelder, J. C., et al.: A.M.A. Arch. Int. Med. 101:658-61, 1958. 3. Frye, W. W., et al.: Am. J. Trop. Med. Hyg. 6:890-93, 1957. 4. Swartzwelder, J. C., et al.: J.A.M.A. 165:2063-67, 1957.

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1. Pagano, P. J.: Med. Times, *86*:1371, 1958.
2. King, J. H., *et al.*: Tr. Am. Acad. Ophth. *59*:759, 1955.

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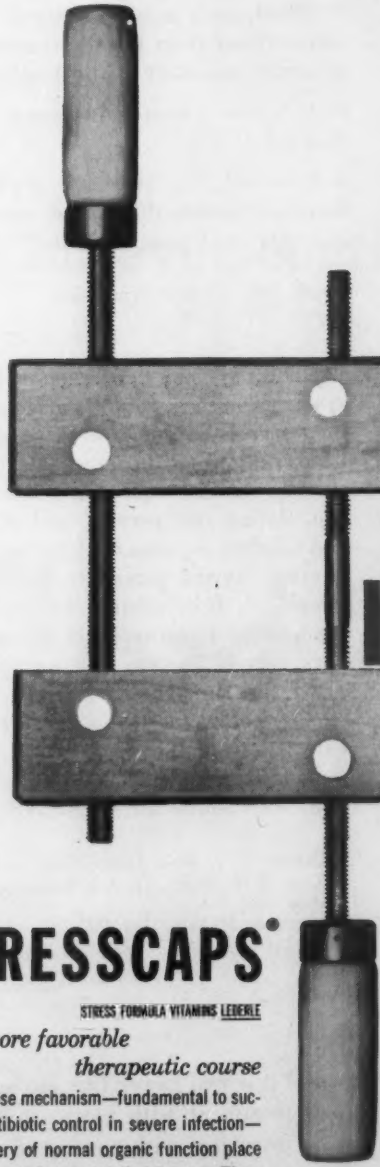

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1. Daskal, H. M.: Antibiotic Med. & Clin. Ther. 2:33 (June) 1956.
2. Pollack, H. and Halpern, S. L.: Therapeutic Nutrition, National Research Council, Washington, D. C., 1952.

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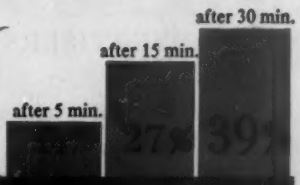

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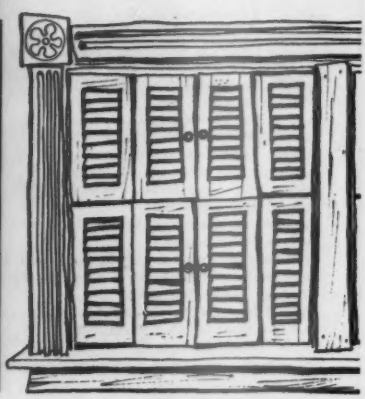

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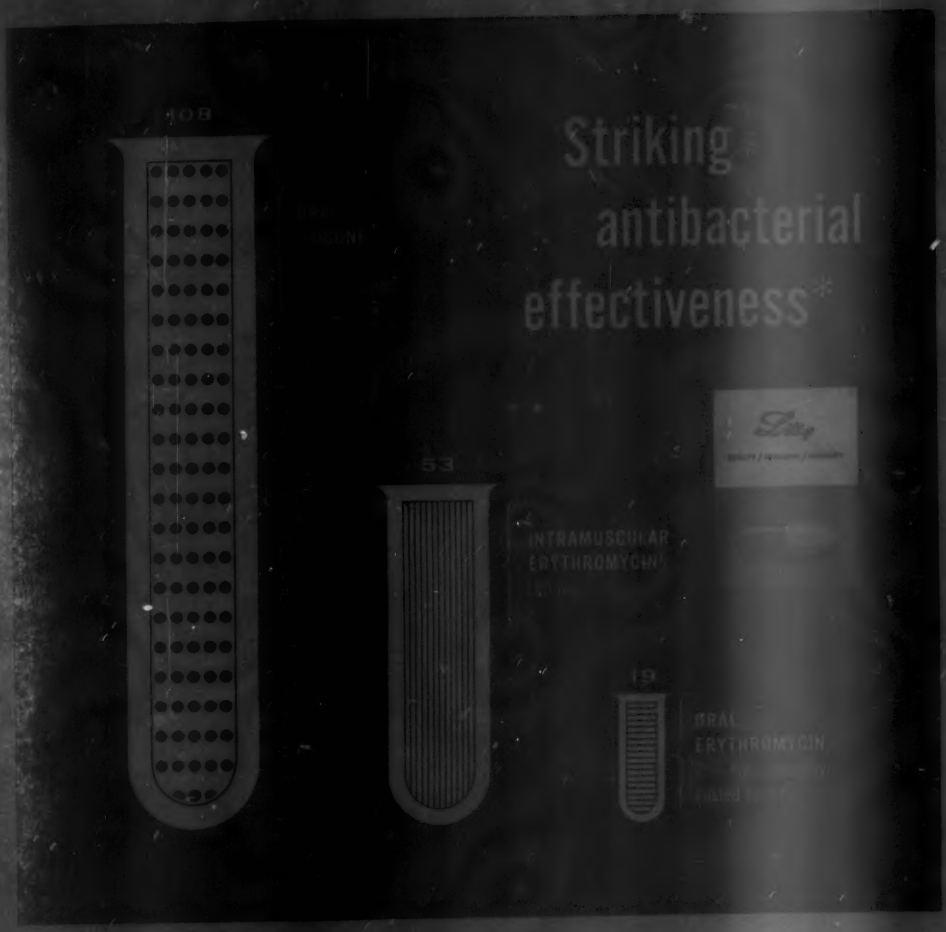

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1. Griffith, R. S., *et al.*: Antibiotic Med. & Clin. Therapy, 5:609 (October), 1958. Note: Peak levels with the oral erythromycin tablets (thirty-three dilutions) were not observed until four hours after administration. 2. Data from Griffith, R. S.: Antibiotics Annual, p. 289, 1954-1955.

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